Washington State Health Care Authority

Continuous glucose monitoring: re-review

Draft report - peer review, comment and response

January 2, 2018

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Continuous Glucose Monitoring: Re-review

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Responses to clinical and peer reviewers

Aggregate Analytics Inc. is an independent vendor contracted to produce evidence assessment reports for the Washington Health Technology Assessment (HTA) program. For transparency, all comments received during public comment periods are included in this document and attachments. Comments related to program decisions, process, policy or other matters not pertaining to the evidence report, are acknowledged through inclusion only and do not require a response from AAI.

Specific responses pertaining to peer reviewer comments are included in **Table 1.**

Draft report peer reviewers:

- Jessica Castle, MD; Assistant Professor of Medicine, Division of Endocrinology, Diabetes and Clinical Nutrition, Oregon Health & Science University School of Medicine
- Ines Guttmann-Bauman, MD ; Associate Professor of Pediatrics, Pediatric Medical Director of the Harold Schnitzer Diabetes Health Center, Oregon Health & Science University

Responses to public comment may be found in **Table 2.**

Full texts of peer reviews, public comments and included references and attachments follow the tables.

Table 1. Responses to Clinical and Peer Reviewers

	Comment	Response
Jessica Castle, MD		
	Specific comments	
Introduction	The topic is appropriate and the public policy and clinical relevance is well defined. It should be made evident that this review does not cover automated insulin delivery, which is an important but separate topic relating to CGM.	Thank you for your comments. We have added a sentence has in several places to make this clarification
Background, ES-1	The paragraph implies that other autoimmune disorders are a complication of diabetes, whereas having one autoimmune disease (such as type 1 diabetes) increases your genetic risk of having a second autoimmune disease.	Thank you for your comments. We have edited the wording.
Background, ES-1	As is mentioned in the document, CGM measures interstitial glucose, so it is more accurate to state it displays the current glucose level (not current blood glucose level, as it does not measure blood glucose). Please remove references to blood glucose in relation to CGM.	Thank you for your comments. We have corrected this.
Background, ES-2	In terms of outcomes, recommend considering time in hypoglycemia and severe hypoglycemia separately.	Thank you for your comments. We have added author definitions and reported these separately in the results.
Background, page 13	Under background, it should be noted that not all patients with type 2 diabetes end up on insulin. Gestational diabetes should be defined separately from diabetes in pregnancy	We appreciate your comments. We have made some edits to the background regarding insulin use in type 2 diabetes. We have also made some edits to further differentiate GDM from pregnancy in those with pre-existing diabetes in the background; Results and data are reported separately for these.
Background, page 16	An A1C of 5.7% or higher is abnormal (not 6%).	Thank you for your comments. We have corrected this.
Background, page 17	Please provider a reference for the comment that a measurement of glucose by the CGM takes 7-15 minutes before it is displayed. I don't believe that is accurate. There is a physiological delay as the report notes, and CGM values in the past were smoothed which imparted a delay (but I believe this smoothing has been removed/minimized with current day devices). The report reads "the FDA has not approved any CGM device for insulin dosing decisions, so persons using CGM must still conduct SMBG several times a day." The Dexcom G5 is	Thank you for your comments. We have made edits to this section and added references. We have corrected this.

	Comment	Response
	approved for non-adjunctive use and the Medtronic 670G system automates insulin delivery based on CGM. Please add a discussion in the executive summary and in the background section on the changing accuracy of CGM from 2011 to now. CGM has changed significantly since 2011 (in terms of user experience and accuracy) and a reader should be aware of that when reading this report. Consider, for example, the average CGM wear time from the landmark 2008 NEJM JDRF trial as compared to the DIAMOND trial.	Additional context has been provided. A table of wear time for included studies has been added to the appendices.
Report Objectives & Key Questions	*Aims/objectives clearly address relevant policy and clinical issue?* *Key questions clearly defined and adequate for achieving aims?* Yes, aims and objectives clearly address relevant policy and clinical issues and key questions were clearly defined and adequate for achieving aims.	Thank you for your comments.
Methods, page 64	I think it is useful to consider all available data for CGM, but as described above, making conclusions about current day CGM based on older data, including data from 2008-2012, is problematic.	We appreciate your comments. We have noted which newer devices are represented in included studies. A table of devices (including wear time) used in the included trials is included in the appendices. Many of the older studies are still cited as landmark studies for CGM. There are few trials that have used the newer devices (VanBeers 2016, Beck 2017, Lind 2017 Bolinder 2016, Haak 2016). These studies are labeled in meta-analyses and tables. Some devices represented in other trials published after 2012 appear to still be in use/marketed. All studies are labeled in meta-analyses and tables.
Results, ES-6	The difficulty with reviewing data from 2011-2017 with regards to CGM is that CGM has so drastically changed over this time period with marked improvement and usability. I suggest naming the devices used in the results section as outcomes with the use of an older device, as well as user experience with regards to alarms, usability of the device, and discontinuation rates, may not apply to a newer device given differences in accuracy, ability to share data, and other features.	Thank you for your comments. We have made edits to the executive summary and background describing changes in devices including accuracy. Key points have been edited where appropriate to note results from studies which used newer devices. It is interesting to note that for some outcomes, findings from

	Comment	Response
		such studies did not differ substantially from studies which employed older devices. A table of devices (including wear time and MARD) used in the included trials is included in the appendices. Tables and text in the safety section have been updated to distinguish findings from newer devices. With any systematic review, we realize that data may not fully represent the most recent advances and is a "snap shot" that reflects the currently available published evidence from peer – reviewed literature.
Results, ES-6	Macrovascular complications and fetal outcomes don't really apply to children, so I think those should be removed in the table of ≤18 years of age or notate as no evidence/not applicable.	We appreciate your feedback. We acknowledge that macrovascular outcomes take time to develop. They are considered one of the primary clinical outcomes that are impacted by maintaining appropriate glycemic control. Our search was broad enough to capture the possibility that there may be long-term follow-up from early trials/studies (beyond 12 months) and/or quality observational studies which may provide longer term follow-up or longitudinal assessment that could capture longer-term complications. Lack of longer-term follow-up appears to be needed. Although no literature on persons ≤18 years old that were pregnant was identified, it may be possible for persons in this age group who have diabetes to become pregnant and potentially fetal outcomes may be important.
Results, ES-7	In the result table starting on page ES-6, time in hypoglycemia should be considered separately from severe hypoglycemia. The latter occurs much less frequently, and studies are often not powered to detect a difference for this	Thank you for your comments. The table wording has been amended and we have made edits throughout the report to separate

	Comment	Response
	less frequent event. The field is coming to a consensus that time <70 mg/dL should also be considered separately from <54 mg/dL, although those metrics are not available from many past studies.	and clarify these ranges and to distinguish time spent in the range(s) from severe hypoglycemic events
Results, ES-9	Severe hypoglycemia is defined by the American Diabetes Association as requiring assistance from another individual. So I would not use that term for < 55 mg/dL. In a recent consensus paper (reference below), glucose <54 mg/dL was defined as Level 2 hypoglycemia. Discussion of hypoglycemia throughout the document needs to be revised to be clear on percentage of time <54 mg/dL and episodes of severe hypoglycemia (such as a hypoglycemic seizure), as these are two different outcomes. It would be useful to reference which study is being described in the summary of results in the event a reader wants to find more information. A simple number reference corresponding to the reference listed at the end would suffice. *Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, Kowalski AJ, Madden P, McAuliffe-Fogarty AH, McElwee-Malloy M, Peters A. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017 Dec 1;40(12):1622-30*	We appreciate your comments. Definitions of severe hypoglycemia used in various trials were verified and described more fully in the results; not all trials report "severe" hypoglycemia provided definitions. None of the trials used the terminology categorizations for level 1 and level two described in the recent consensus paper; we have given the ranges for the different levels. The Agiostratidou paper indicates that there is not consensus regarding the amount of time at a particular blood glucose level to be considered in level 1 or level 2 hypoglycemic range . References for the studies in the bullet Key Points are included in the Summary of evidence tables.
Results, ES-14	The report reads "Adults with type 1 DM not taking prandial insulin." Should this read type 2 DM?	Thank you for your comments. This has been corrected.
Conclusions, page 158	At the beginning of table 5.1.1, CGM is labeled GCM, which may confuse readers.	Thank you for your comments. This has been corrected.
Conclusions, page 158	It would be worthwhile to highlight the conclusions based on recent data (for example only studies using Dexcom G4 with software 505 algorithm, G5, Enlite or Guardian 3). As noted above, data published in 2008 likely does not reflect results obtained with current day sensors.	Thank you for your comments. Please see previous responses. We have made edits to the executive summary and background describing changes in devices and accuracy. Key points have been edited where appropriate to note results from studies which used newer devices. It is interesting to note that for some outcomes, findings from such studies did not differ

	Comment	Response
		substantially from studies which employed older devices
Conclusions, page 160	As noted above, severe hypoglycemia is defined as requiring assistance from a third party, not a glucose of 55 or less.	Thank you for your comments. We have clarified ranges for hypoglycemia and definitions of severe hypoglycemia throughout the document
Overall Presentation & Relevancy, General Comments	I have no concerns about the overall presentation and the topic is very relevant to clinical medicine and public policy/public health.	Thank you for your comments.
Quality Rating	**Quality of Report** Superior **0** Good **1** Fair **0** Poor **0**	
Ines Guttmann-Bauman, MD		
	Specific comments	
Introduction, Public Policy and Clinical Relevance, General Comments	*Overview of topic is adequate*? *Topic of assessment is important to address*? Yes *Public policy and clinical relevance are well defined?* In general, it is well defined. However, I would think it is important to emphasize the difference between insulin requiring and non-requiring diabetes. Utilizing insulin might contribute to wider fluctuations of blood glucose and in such cases there might be a bigger benefit of using the CGM. This is particularly important for the group under 18 years old, which largely comprises of insulin-dependent patients.	Thank you for your comments. We have added additional context to the introduction.
Introduction, Page 5 Line starting from 1 – Outcomes assessed	I am challenged by the definition of primary outcomes, as microvascular and macrovascular complications take many years to develop, and cannot be assessed adequately by a study 6 -12 months long. Fetal outcomes and c-section rates are a bit more appropriate primary outcomes, as they can be reasonably linked to intervention. However, those are the more accepted markers of overall diabetes control, and I can see why they are listed as primary outcomes, despite the fact they could not be addressed in any analysis to date.	Thank you for your feedback. We acknowledge that such outcomes may take time to develop and were considered the primary clinical outcomes that are impacted by maintaining appropriate glycemic control. Our search was broad enough to capture the possibility that there may be long-term follow-up (beyond 12 months) to older trials and/or quality observational studies which may provide longer term follow-up or longitudinal assessment that could capture longer-term complications.

	Comment	Response
		Longer-term follow-up appears to be needed.
Background, General Comments	*Content of literature review/background is sufficient?* This section is very comprehensive and summarizes not only the rationale for CGM use but gives a good review of current professional societies recommendations and insurer coverage. I find it to be useful in illuminating the differences between the entities quite well. I have no specific objections to the Background session.	Thank you for your comments.
Report Objectives and Key Questions, General Comments	*Aims/objectives clearly address relevant policy and clinical issue?* Agree. *Key questions clearly defined and adequate for achieving aims?* Agree.	Thank you for your comments.
Methods, General Comments	*Method for identifying relevant studies is adequate?* Yes *Criteria for the inclusion and exclusion of studies is appropriate?* Yes *Method for Level of Evidence (LoE) rating is appropriate and clearly explained?* Yes *Data abstraction and analysis/review are adequate?* Yes	Thank you for your comments.
Methods, Page 59, Line 14 onwards	Articles selected for full text review refer to chronic migraine, chronic tension-type headache and chronic daily headache. This might be a copy-paste type error.	Thank you for your comments. We have corrected this.
Results, General Comments	*Amount of detail presented in the results section appropriate?* Yes *Key questions are answered?* Yes *Figures, tables and appendices clear and easy to read*? Yes *Implications of the major findings clearly stated*? Yes *Have gaps in the literature been dealt with adequately?* Yes *Recommendations address limitations of literature?* Yes, very clearly	Thank you for your comments.
Conclusions, General Comments	*Are the conclusions reached valid?* Yes	Thank you for your comments.
Overall Presentation and Relevancy	*Is the review well-structured and organized?* *Are the main points clearly presented?* *Is it relevant to clinical medicine?* *Is it important for public policy or public health?* The answer to all of the above is certainly yes. The authors performed a thorough literature search, reviewed and	Thank you for your comments.

	Comment	Response
	graded the evidence appropriately. Unfortunately, the quality of evidence is predominantly low to moderate, which illustrates current limitations of research in this field. One of the important clinical points is that benefits with CGM usage increase with increased frequency of wearing the device, and the authors of this review did highlight it when the results of individual studies suggested the effect. Clearly, there is a need for studies that will address this variable more consistently and hopefully in more detail. It is unfortunate that this review occurred prior to publication of the "Diabetes Care" December 2017 issue, as they thematically dedicated a part of it to the review of CGM systems. It contains several relevant new consensus papers. However, my review of references used for position papers reveals no relevant studies that might have made a difference in conclusions of this review. Lastly, in the same issue of "Diabetes Care", there is a call for taking outcomes other than A1c into account when evaluating both clinical care and research. One of the measures that was introduced as needing more emphasis is "time in range", which can be assessed with the help of CGM technology. I hope this will provide the community of endocrinologists with more relevant data and further illuminate the role CGM plays in achieving optimal diabetes outcomes.	We are pleased to note that relevant papers were included in our report. We have included the Danne 2017 clinical consensus statement from this issue into the report background. We do report information on time spent in hypoglycemic (primary intermediate outcome) and hyper glycemic ranges (secondary outcome) as available from included trials. Time spent in a target range was not uniformly reported across trials and was not a specified outcome for this report. We have included information on this intermediate outcome in the data abstraction tables by study in the appendices and in a separate appendix.
Quality Rating	**Quality of Report** Superior **1** Good **0** Fair **0** Poor **0**	

Responses to public comment on draft report

This second section responds to comments received during the public comment period from the following:

- Fran Broyles, M.D., Medical Director Diabetes, Endocrinology and Nutrition, Swedish Medical System
- Jonathan D. Leffert, MD, FACP, FACE, ECNU, President of American Association of Clinical Endocrinologists (AACE)
- Cindy Brinn, RD, CDE, BC-ADM; PeaceHealth Medical Group Nutrition & Diabetes Educator
- David Turk, M.D, Endocrinology
- David A. Price, MD; Vice President, Medical Affairs, Dexcom, Inc.
- Michael Bolen, Director, State Government Affairs, Medtronic
- Irl B. Hirsch, MD, Professor of Medicine, University of Washington School of Medicine
- Cate Pihoker, MD, Professor of Pediatrics, University of Washington & Craig Taplin, MD, Associate Professor of Pediatrics, University of Washington
- Alyson K Blum, PharmD, CDE, Sacred Heart Center for Maternal Fetal Medicine Diabetes Care Team
- Lawrence T. Smith, President, National Diabetes Volunteer Leadership Council
- Refaat Hegazi, MD, PhD, MS, MPH & Shengsheng Yu, PhD; Abbott Diabetes Care
- Lindsey De Koster

Complete comments submitted and associated data are attached following the responses below.

Table 2. Responses to public comments

	Comment	Response
Fran Broyles, M.D., Medical Director Diabetes, Endocrinology and Nutrition, Swedish Medical System		
	Specific comments	
	We desperately are in need of coverage for the Dexcom CGM for Type 1 Diabetics with hypoglycemic unawareness on Medicaid. This is lifesaving and saves hundreds of thousands of dollars by avoiding ER visits, hospitalizations, 911 calls missed work and office visits. Please consider this VERY important device approval.	Thank you for your comments. Comments related to the Health Technology Assessment Program and policy process or decisions by the Health Technology Clinical Committee do not require a response from the evidence vendor, Aggregate Analytics, Inc.
Jonathan D. Leffert, MD, FACP, FACE, ECNU, President of American Association of Clinical Endocrinologists (AACE)		
	Specific comments	
General Comments, Submission of AACE Consensus Statement on Outpatient Glucose Monitoring	On behalf of the American Association of Clinical Endocrinologists (AACE), we would like to applaud the Health Technology Clinical Committee (HTCC) consideration of coverage for continuous glucose monitoring (CGM) in the Washington state Medicaid program. AACE represents more than 7,000 endocrinologists in the United States and abroad, including over 400 clinical endocrinologists in the State of Washington. AACE is the largest association of clinical endocrinologists in the world. The majority of AACE members are certified in Diabetes, Endocrinology and Metabolism and concentrate on the treatment of patients with endocrine and metabolic disorders including diabetes, thyroid disorders, osteoporosis, growth hormone deficiency, cholesterol disorders, hypertension and obesity. As you deliberate coverage criteria for this important technology, AACE hopes you will consider the attached AACE and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement, which makes recommendations regarding the appropriate patient population to utilize CGM. Utilization of CGM among patients with diabetes, both type 1 and	Thank you for your comments. Our report includes the mentioned consensus statements in section 2.3.

	Comment	Response
	type 2, undergoing a regime of intensive insulin therapy has shown demonstrated efficacy in reducing hemoglobin A1C, the measure of blood sugar control. Improvement in blood sugar control will result in decreased complications of this dreaded disease. CGM reduces severe hypoglycemic episodes. Reduction in severe hypoglycemia episodes can decrease ER visits, accidents on highways, and even death. A broad CGM coverage decision by Washington state's Medicaid will enable physicians to prescribe CGM for their appropriate patients, thus increasing population health and reducing costs in the Medicaid system. Once again, thank you for your decision to review coverage for CGM to the Washington state Medicaid population, AACE looks forward to your final decision.	
Cindy Brinn, RD, CDE, BC-ADM; PeaceHealth Medical Group Nutrition & Diabetes Educator		
	Specific comments	
	Dear Washington State Medicaid Decision Makers, I have been a diabetes educator for nearly 40 years and the diabetes technology options that have surfaced during the past three years are improving the health of our patients with diabetes. The continuous glucose monitors dramatically reduce the risk of low blood glucose episodes and complications and hospitalizations and improve A1c values by reducing blood glucose elevations. The reduction in high and low blood glucose numbers saves lives and reduces costs significantly in our patients with diabetes. The magic of continuous glucose monitoring devices (dexcom) and the Medtronic 670G insulin pump with continuous glucose monitor has helped patients know in REAL time when their blood glucose is rising or high or dropping or low. They get ALERTS about what is happening and can respond appropriately with appropriate treatment of the low	Thank you for your comments. Comments related to the Health Technology Assessment Program and policy process or decisions by the Health Technology Clinical Committee do not require a response from the evidence vendor, Aggregate Analytics, Inc.

	Comment	Response
	blood glucose or an insulin injection for a high blood glucose. The finger stick glucose monitoring seems so archaic when compared to these new continuous options. Persons with diabetes requiring insulin need to CONTINUOUSLY know what their blood glucose is to best manage their diabetes and prevent dangerous complications. I have numerous Molina insured adults that are using very successfully the dexcom sensor and will find it devastating to not have this device available to them any longer. There will certainly be increased low blood glucose episodes and costs for my patients if this device is no longer covered for them. I urge you not move backwards with the management of our patients with diabetes and to CONTINUE the coverage of the dexcom sensor and consider coverage of the 670G insulin pump and sensor. They are absolutely cost effective. Medicare is covering the device! Thanks for your serious consideration of this cost effective and life changing technology for our Washington Molina patients. Kind Regards, Cindy Brinn	
David Turk M.D., Endocrinology		
	Specific comments	
	Dear Washington State Medicaid Decision Makers, I am an Endocrinologist in Bellingham, WA. I have been working in this community for the last 23 years. My diabetic practice is quite large. This letter is in response to the recent decision to stop providing continuous glucose monitoring systems (dex com) to adult patients. The most useful diabetic tool developed in the last 20 years has been the continuous glucose monitor (dex com). This device	Thank you for your comments. Comments related to the Health Technology Assessment Program and policy process or decisions by the Health Technology Clinical Committee do not require a response from the evidence vendor, Aggregate Analytics, Inc.

	Comment	Response
	measures the blood sugar in real time, continuously day and night. It also alerts patients when the blood sugar is high or low and tells the patient whether the glucose level is rising or falling. This device is becoming standard of care – Medicare is now covering its use. The continuous glucose monitor has revolutionized so many of my patients' lives. They have been able to move from having hypoglycemic episodes, medic calls, emergency room visits, hospitalizations, and sometime even seizures from the low blood sugars to a much more normal life and better diabetic control. If they are not allowed to continue the use of the CGMS, their lives will be devastated. I cannot explain how difficult this will be for these individuals. Considering the cost of medic visits, ER visits for low blood sugars, possible hospitalizations, and complication of diabetes, I cannot believe the CGMS is not a positive with regards to cost. I ask that you reconsider the decision to not cover CGM systems (dex com) for adults. I believe that decision is a step backward in diabetic care. Thanks you for your consideration. Sincerely, David Turk M.D	
David A. Price, MD; Vice President, Medical Affairs, Dexcom, Inc.		
	Specific comments	
Overall, Summary of Comments	Dear members of the HTCC: On behalf of Dexcom, Inc., I am writing to express my appreciation for selecting continuous glucose monitoring (CGM) for re-review and the opportunity to provide a rebuttal to aspects of the *CGM Update – Draft Evidence Report (November 2017)*. With this letter, I would like to provide some initial general comments followed by more specific remarks.	Thank you for your comments. As a point of clarification the HTCC did not formulate the evidence report. The report is formulated by Aggregate Analytics, an independent evidence synthesis vendor. Comments related to policy or formulation of policy by the HTCC are included for completeness but do not require a response by the vendor.

	Comment	Response
	Although the analysis conducted by the HTCC is quite extensive, I am not confident that the conclusions reached by the committee are relevant to current CGM technology. Because it is generally impractical to study the impact of diabetes treatment on long-term microvascular and macrovascular complications (as such studies must be conducted over many years and require very large samples), change in hemoglobin A1c (HbA1c) is recognized as the standard outcome in diabetes treatment clinical trials due to its strong association with long-term diabetes complications. Additional blood glucose metrics, such as time spent in the target glycemic range and time spent in hypoglycemia, are being increasingly recognized as clinically relevant diabetes treatment outcomes. Therefore, it is important to understand how CGM technology impacts these metrics. Our main current concerns are summarized as follows: 1. Information included in our prior correspondence regarding the Washington HTA has not been incorporated into this analysis. 2. The review applies pharmaceutical evaluation standards to CGM, a rapidly evolving technology, which many be inappropriate and likely underestimates the clinical value of CGM.[1] By basing its conclusions on studies that evaluated now obsolete CGM technology (i.e., devices that have not been commercially available for many years), the HTCC underestimates the clinical benefits of the most current CGM technology. 3. The review fails to recognize the clinical significance of a variety of outcomes from recently completed randomized controlled trials (RCTs) using current-generation CGM and excludes a recent RCT that evaluated the impact of CGM in adults with insulin-treated type 2 diabetes (T2D).	Thank you for your feedback. We acknowledge that such outcomes may take time to develop and were considered the primary clinical outcomes that are impacted by maintaining appropriate glycemic control. Our search was broad enough to capture the possibility that there may be long-term follow-up (beyond 12 months) to older trials and/or quality observational studies which may provide longer term follow-up or longitudinal assessment that could capture longer-term complications. Longer-term follow-up appears to be needed. Time spent at hypoglycemic thresholds (and hyperglycemic thresholds), area under the curve and other outcomes are provided in the report. A summary of time spent in the target range is summarized in the Appendices. 1. Comments (including all attachments) provided by the HTA program during topic nomination as well as in response to posting of key questions were reviewed by AAI prior to report formulation. AAI's response to comments is found at: https://www.hca.wa.gov/assets/program/cgm-draft-key-qs-comment-response-20170918.pdf Briefly, all guidelines mentioned in Dexcom's previous comments are included in the report, all studies cited were reviewed and if they met the *a priori* inclusion criteria were included in the draft report. 2. Methods used for this review are consistent with those used by the Cochrane Collaboration and Agency for Healthcare Research and Quality and guidelines suggested by the National Academy of Medicine (formerly the Institute of Medicine) for systematic reviews; These standards are used for

	Comment	Response
	Additionally, the Washington HTA fails to recognize the unique FDA approval and CMS classification of the Dexcom G5 Mobile CGM System as replacement for self-administered blood glucose monitoring (SMBG) in diabetes treatment decisions. In addition to these major concerns, the HTA assessment fails to recognize the clinical significance of reduction in time spent in hypoglycemia, particularly at night; the demonstration of CGM clinical benefits in patients with both type 1 diabetes (T1D) and T2D; and recently updated professional society recommendations for improved access and benefits of CGM therapy.[2-4] There is evidence that current-generation CGM therapy is cost effective in the short term by reducing the incidence of costly emergency medical treatment of severe hypoglycemia[5] and in the long term by decreasing the risk of microvascular and macrovascular complications.[6]	devices, including evolving technologies, as well as pharmaceuticals. With any systematic review, we realize that data may not fully represent the most recent advances and is a "snap shot" that reflects the currently available published evidence from peer –reviewed literature. We have added context to executive summary and background describing changes in devices including accuracy. Few trials on newer devices have been published; many older trials are considered pivotal trials and are cited in guidelines and consensus statements relating to the use of CGM. Some of the devices used in some later trials appear to still be commercially available and marketed even though they do not incorporate the most recent technology. Key points have been edited where appropriate to note results from studies which used newer devices. A table of devices (including wear time and MARD) used in the included trials is included in the appendices. Tables and text in the safety section have been updated to distinguish findings from newer devices where data are available. It is interesting to note that for some outcomes, findings from such studies did not differ substantially from studies which employed older devices. 3. Three trials of traditional CGM in persons with T1D using more current devices were included in the DRAFT report (Beck 2017, Lind 2017, van Beers 2016). If these would be the only trials considered, evidence would be limited. In both the draft and final reports, time spent at hypoglycemic thresholds (and hyperglycemic thresholds), area under the curve and other outcomes are provided in the report. For some outcomes, effect estimates from newer devices are consistent with those from older trials using older devices. The Beck 2017 trial in T2D has been added; the

	Comment	Response
		overall conclusions were not substantially impacted by its addition. In both the draft and final reports, the Dexcom G5 CCM is listed as not requiring SMBG for treatment decisions. Nocturnal hypoglycemic outcomes (time spent in range, AUC) as reported in included trials are included in the both the draft and final reports for T1D and T2D. Guideline publications cited are in both the DRAFT report and the final report as it the Chaugle 2017 economic study cited. The other citation (Bronstone 2016) did not meet inclusion criteria.
Therapeutic CGM	The CGM Update – Draft Evidence Report (November 2017) includes contradictory statements about the status of FDA-approved CGM devices for replacement of SMBG for therapeutic decision making. Specifically, on page 17, the report incorrectly states that "The FDA has not approved any CGM device for insulin dosing decisions, so persons using CGM must still conduct SMBG several times a day." On page 19, the report correctly states that "The Dexcom G5 Mobile CGM System is the only real-time CGM device approved for therapeutic decision making, as a replacement of traditional finger stick SMBG." FDA approval of the Dexcom G5 Mobile System as a replacement of SMBG for therapeutic decision making was made in December 2016 based on the recommendations of a full FDA panel hearing.7 In addition, results from the REPLACE-BG study,8 a multicenter, randomized, noninferiority clinical trial, confirmed that the use of CGM without confirmatory blood glucose monitoring measurements is as safe and effective as using CGM adjunctive to blood glucose monitoring in well-controlled adults with T1D. In the REPLACE-BG trial, subjects used a Dexcom CGM system running the software currently available in our Dexcom G5 Mobile CGM system. Study results showed that CGM without confirmatory blood glucose monitoring is as safe and effective as using CGM adjunctive to blood glucose monitoring or confirming with a fingerstick and blood glucose meter before	Thank you for your comments. We have corrected the statement/section. The reference #8 (Aleppo 2017) did not meet our inclusion criteria. As stated previously, additional context regarding improved accuracy of CGM devices has been added to the report and a table which includes MARD information has been added to the appendices. The CMS policy is cited (draft and final reports) in section 2.5 and context related to therapeutic vs. adjunctive devices has been added. The vendor is only required to provide information on CMS National Coverage Decisions and from 2 bell-weather payers. The LCD has not been included in the report.

	Comment	Response
	making a diabetes treatment decision.8 Thus, patients using the Dexcom G5 Mobile CGM can reduce their burden of multiple daily finger sticks when using CGM without loss of efficacy or safety. The demonstrated best-in-class accuracy of the Dexcom G5 Mobile System, coupled with the ability to set real-time hypoglycemic and hyperglycemic alerts, allows it to provide patients and caregivers with a superior method of managing their diabetes care compared to conventional blood glucose monitoring (SMBG). When discussing the accuracy of CGM, it is helpful to understand the terms involved. Overall accuracy of CGM is measured by the mean absolute relative difference (MARD), which represents the difference between CGM readings and contemporaneous blood glucose values assessed by a laboratory standard. A recent study that evaluated the accuracy of 17 point-of-care SMBG blood glucose meters found that the MARD for the glucose meters ranged from 5.6% to 20.8%, with 9 of the 17 meters having a MARD exceeding 10%.9 In assessing the safety of insulin dosing based on CGM data, the threshold for accuracy has been recognized at less than 10%.10 The Dexcom G5 Mobile has an overall MARD of 9.0%. In 2017, the Centers for Medicare and Medicaid Services (CMS) announced the benefit category of non-adjunctive or "therapeutic" CGM. This provided a categorization for both non-therapeutic and therapeutic CGM, with the latter defined as devices that can be used to replace fingerstick blood glucose testing for diabetes treatment decisions.11 Such systems are classified as durable medical equipment within the scope of Medicare Part B. Currently, Dexcom G5 Mobile is the only device which meets the therapeutic CGM device classification. On May 18, 2017, a Local Coverage Determination (LCD) for glucose monitoring and Related Policy Article were revised to reflect the CMS ruling.12 Per the LCD, therapeutic CGM may be covered by Medicare when the beneficiary has diabetes and meets all of the following criteria:	

	Comment	Response
	• Has been using a blood glucose meter (BGM) and performing frequent (4 or more times a day) testing; • Is insulin-treated with MDI or a Medicare-covered CSII pump; • The insulin regimen requires frequent adjustment on the basis of BGM or CGM testing results; • Within 6 months prior to ordering the CGM, the treating practitioner has an in-person visit with the beneficiary to evaluate their diabetes control and determined that criteria are met; and • Every 6 months following the initial prescription of CGM, the treating practitioner has an in-person visit with the beneficiary to assess adherence to their CGM and treatment plan.	
Use of Meta-Analysis to Evaluate CGM	As mentioned in previous correspondence with the Washington Health Care Authority, experts note that meta-analysis is an inappropriate approach to evaluating rapidly evolving technologies, such as CGM, and may significantly underestimate the efficacy and utility of current CGM systems in diabetes management.1 CGM is not analogous to a drug which remains the same molecule in all studies. In contrast, CGM technology is constantly evolving, with newer devices having significantly improved accuracy, performance, comfort, and usability compared with older devices (Figure 1). These iterative improvements in technology have resulted in unprecedented high levels of CGM utilization and patient satisfaction.13-15 In the recent Diamond and Gold studies,13-15 patient ratings of satisfaction with CGM and CGM utilization rates were much higher than were previously seen in the JDRF clinical trials completed almost a decade ago.16,17 Numerous studies have shown that consistent use of CGM is essential for maximum clinical benefit.18-23 Thus, it is reasonable to conclude that problems associated with early-generation CGM devices may have resulted in poor protocol compliance and distorted the conclusions of such studies as to the magnitude	Thank you for your perspective. Methods used for this review, including those for meta-analysis, are consistent with those used by the Cochrane Collaboration and Agency for Healthcare Research and Quality; these organizations have applied meta-analytic methods to topics related to diabetes care. Some of the objections to meta-analysis in articles questioning the value of meta-analysis for diabetes technologies have to do with failure to use such methods. Data available for this report were insufficient to do meta-regression or stratified analysis. The forest plots include information on baseline A1c and an estimate of CGM adherence (defined in the appendices). Data from the individual trials (Including those using newer devices) are represented in the plots. Information on improved satisfaction with earlier devices in include for context in the report. Secondary outcomes related to quality of life are included in the report. Information on adherence and impact on outcomes is included in the draft and final reports. Most of these data are not comparative (i.e. case series) data from trial extensions.

	Comment	Response
	of the potential clinical benefits or lack thereof of CGM.1 The vast majority of studies included in the meta-analysis conducted by the HTCC evaluated CGM devices that are now obsolete and no longer commercially available. As shown in Table 1, 19 of the 22 RCTs included in the HTCC meta-analysis that evaluated CGM in children, adolescents, and non-pregnant adults with T1D or T2D utilized CGM technology that is now obsolete and associated with MARD values ranging from 13% to 20%. The accuracy of these previous generations of CGM is significantly less than the accuracy of the Dexcom G5 Mobile System (which has a MARD of 9.0%). By including studies that evaluated older CGM technology in the meta-analysis, the HTCC may have significantly underestimated the potential benefits of this therapeutic category and blunted the impact that patients experience from today's CGM technology.	Please see previous comments regarding the inclusion of trials that used older devices; limited data on newer devices is available and for some outcomes examined in the report do not differ substantially from effect estimates from trials using older devices or pooled estimates across trials.
Outcomes in HTTC Meta-analysis, Primary HbA1c Outcome	The HbA1c outcome selected as the primary outcome for the HTCC meta-analysis is the proportion of patients achieving an HbA1c level of <7.0% at study end. It is noteworthy that this outcome was not the primary endpoint in any of four RCTs included in the meta-analysis of this outcome. Current American Diabetes Association (ADA) guidelines stress the importance of setting individual patient goals for target HbA1c.[2] The ADA guidelines state that, although a reasonable HbA1c goal for most nonpregnant adults is <7.0%, "more or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations."[2] Thus, defining a "successful" outcome as achieving HbA1c <7.0% is inconsistent with current national diabetes guidelines. Although the primary endpoint in CGM trials has varied across studies, mean change in HbA1c from baseline is the most commonly specified primary endpoint in RCTs of CGM. A 1% reduction in HbA1c has been associated	Thank you for your comments. The primary outcomes identified *a priori* (listed in the public key question document and draft report) were not restricted to achieving target of <7% for A1c. This was the most commonly reported threshold in included studies. Data provided by trials for any "success" threshold are reported as were changes in mean A1c and time spent at various glucose thresholds as stated previously. Authors for various trials may not have considered these to be primary outcomes. Studies cited by commenter were included if they met our inclusion criteria. Reasons for exclusion at full text review are included in the appendices.

	Comment	Response
	with both short-term reductions in healthcare utilization and costs and risk of long-term diabetes complications. In a retrospective analysis of administrative data from a large Washington state health maintenance organization, patients with diabetes who achieved a 1% sustained reduction in HbA1c had statistically significant annual cost savings of $685-$950 per patient in the subsequent year.[24] A 1% reduction in HbA1c reduces diabetes-related deaths by 21%, risk of microvascular complications by 37% and myocardial infarction by 14%.[25] We note adults with T1D who received CGM in the Diamond Study reduced their HbA1c by 1% on average.[13]	
Outcomes in HTTC Meta-analysis, Time in Nocturnal Hypoglycemia	**Time in Nocturnal Hypoglycemia** The HTTC meta-analysis found that, across parallel and crossover trials, CGM appears to be associated with decreased time spent in hypoglycemia at night compared with SMBG. The Committee noted that the clinical significance of this benefit was unclear. In children with diabetes, nocturnal hypoglycemia is very frequent, mostly asymptomatic, and often prolonged (lasting 1-3 hours).[26] Given that an alarm triggered by a CGM low blood glucose reading may be the only way of alerting children and parents of nocturnal hypoglycemia, reducing time spent in nocturnal hypoglycemia is a critical outcome of diabetes management and a clear benefit of CGM. Hypoglycemia remains the number one barrier to achieving glycemic control and the risk associated with hypoglycemia cannot be understated.[27] The Diamond and Gold trials demonstrated significant impact in the reduction of hypoglycemia through the use of CGM,[28,15] but this benefit was lost when CGM was discontinued.[29] Reduction in the rate of severe hypoglycemia due to CGM is difficult to quantify in RCTs as patients who are at high risk for these events are generally excluded from RCTs and enrolled patients take actions to avoid these events. Designing RCTs adequately powered to detect a statistically significant reduction in the rate of severe hypoglycemia is problematic due to the relative infrequency of severe events and the need for a very large sample size. However, we feel the following	Thank you for your comments. We recognize that time in hypoglycemic ranges is clinically important and that decreasing time in those ranges is important. What is unclear is whether some of the effect sizes (e.g. mean differences) are clinically important. The December issue of Diabetes Care focused on issues and gaps in evidence related to CGM; one article states: …" there is no consensus on how long an individual must remain at a particular blood glucose level to be considered in the level 1 or level 2 hypoglycemic range…" Agiostratidou, G, et. al *(Diabetes Care 2017;40:1622–1630)* Data on nocturnal hypoglycemia from all included trials in the report. While RCTs may not have the power to detect rare events, the literature search was broad; given that CGM has been used for over a decade, we searched for observational studies that might provide such information. Information from identified observational studies is included in the full report.

	Comment	Response
	references should be included when assessing impact of CGM on hypoglycemia and other aspects of diabetes clinical care.	
Most Recent Clinical Evidence, Randomized Controlled Trials Adults with T1D	Several recent studies that used current-generation Dexcom CGM systems have added to the already compelling data establishing the benefit of CGM in patients with inadequately-controlled T1D (HbA1c >7.5%). The DIAMOND prospective, randomized, controlled trial (NCT02282397) examined the effects of CGM use in patients (n=158) with HbA1c values ranging from 7.5% to 9.9% in 24 sites across the United States.[13,30] Subjects randomized to CGM demonstrated consistent and sustained use of the technology at 6 months (93% used it 6 or 7 days/week). Use of CGM resulted in a mean HbA1c decrease of 1.0% from baseline at week 24 compared to a 0.4% reduction in the control group. Subjects in the CGM group spent less time in hypoglycemia and experienced significant reductions in diabetes distress and fear of hypoglycemia, and significant improvements in hypoglycemia confidence and well-being, compared with conventionally-monitored patients. Similar benefits were observed across all patient subgroups, including people with lower education levels, lower numeracy skills, higher baseline HbA1c levels, and older ages. An optional 6-month extension phase offered to people who had used CGM during the index RCT studied the impact of insulin delivery method (MDI versus continuous subcutaneous insulin infusion or CSII) on HbA1c.[28] Results showed that transitioning from MDI to CSII therapy increased time in the target glycemic range, but did not result in a corresponding improvement in HbA1c and increased biochemical hypoglycemia. Subjects in the extension phase continued to use the CGM systems at least 6 days per week. The GOLD study (NCT02092051) also evaluated the effects of CGM in adults with inadequately-controlled T1D who were being treated with MDI. CGM use was associated with a mean HbA1c level that was 0.43% less than conventional treatment. The GOLD study also demonstrated significant improvements in subjective well-being and treatment satisfaction	Thank you for your comments. Studies cited by commenter were included if they met our inclusion criteria. Reasons for exclusion at full text review are included in the appendices. The DIAMOND and GOLD trials were included in the report. Studies comparing insulin delivery methods were not part of the scope for this report

	Comment	Response
	for subjects using CGM compared with conventional therapy. A separate analysis confirmed that CGM reduced time spent in nocturnal and daytime hypoglycemia and increased confidence in avoiding hypoglycemia and hypoglycemia-related problems. [15,29]	
Most Recent Clinical Evidence, Randomized Controlled Trials Adults with Insulin-treated T2D	The DIAMOND study included an independently-powered arm that investigated the effects of CGM in patients using MDI therapy to manage their type 2 diabetes (T2D).14 The results demonstrated that after 24 weeks, participants using CGM lowered their HbA1c levels by an average of 0.8% from baseline. Compared to the control group, the CGM group also spent less time in hyperglycemia and more time spent in the target range. The CGM group increased time in range by 1.3 hours compared to baseline, and 0.6 hours compared to the control group. The HbA1c reductions did not depend on age, educational attainment, or numeracy skills, and adherence to CGM therapy was remarkably high, with 93% of participants using CGM 6 or 7 days per week at the end of the study. Participants also reported a high level of satisfaction and a relatively low level of perceived hassles. The results of this study were not included in the HTCC CGM Update.	The Beck 2017 in T2D has been included in the final report.
Most Recent Clinical Evidence, Randomized Controlled Trials, Children and Adolescents with T1D	The T1D Exchange Clinic Registry follows over 26,000 patients with T1D, almost 15,000 of whom are younger than 18. Recent Registry publications have confirmed that CGM use is increasing rapidly, especially among very young children. The mean HbA1c values among CGM users and non-users in the Registry were recently reported as 8.1% and 8.9%, respectively.[31] CGM use in every age cohort examined was associated with lower HbA1c values, as shown in Figure 2.[32] Separate data from two sensor accuracy studies in youth ages 2-17 years[33] showed that use of CGM had the potential to increase glucose time in range and improve glycemic outcomes.	Observational studies (including registry studies) were included based on the PICOTs inclusion/exclusion criteria established *a priori.* Extensions of RCTS that were observational were included (including Polosky WH, *Diabetes Care* 2017; 40:736-41 listed in the references) Studies from the T1D exchange and other observational studies that met out inclusion criteria are contained in the report. Meeting abstracts or posters were excluded.
Real-World Studies	Data from two recently published real-world studies show that CGM used in conjunction with MDI is as effective as the combination of CGM and CSII therapy for improving glycemic control. The COMISAIR study was a nonrandomized, prospective, real-life clinical trial in which T1D	Comparison of insulin delivery systems was not part of the scope of this report.

	Comment	Response
	patients received MDI or CSII therapy in combination with either CGM or SMBG.[34] Both insulin delivery modalities combined with CGM provided significant and comparable decreases in HbA1c with concurrent reduction in time spent in hypoglycemia compared to insulin therapy with conventional blood glucose monitoring after 1 year. The COMISAIR study followed some patients for up to 2 years, and the recently-reported results from this long-term study confirmed the durability of the HbA1c benefit for users of CGM, regardless of insulin delivery method.[34] An analysis of data from the T1D Exchange registry examined the impact of CGM on HbA1c in 17,731 T1D patients treated with MDI or CSII.[35] Among CGM users, mean HbA1c was similar in the MDI and CSII groups (7.6% vs. 7.7%, P=0.82); however, HbA1c in both CGM groups was lower than among patients using CSII + SMBG (8.3%, P<0.0001) and MDI + SMBG (8.8%, P<0.0001). Results were similar in adults and youth (Figure 3).	
Professional Society Recommendations	The rapid adoption and proven benefits of CGM have prompted several professional societies to issue position statements or consensus recommendations regarding its use in of several professional societies. The American Diabetes Association recognizes that success with CGM depends in part on consistent use and asserts that CGM, in conjunction with intensive insulin therapy, is a useful tool to lower HbA1c in adults (ages ≥25 years) with T1D and can be helpful in lowering HbA1c in children, teens and younger adults.[2] A consensus statement from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology states that CGM should be available to all insulin-using patients regardless of diabetes type.[36] The AACE outpatient glucose monitoring consensus statement recommends personal CGM for patients with T1D diabetes and with history of severe hypoglycemia or hypoglycemia unawareness, and to assist in the correction of hyperglycemia in patients not at goal. [3] The Endocrine Society recommends CGM for adult patients with T1D whose HbA1c is above 7% who are able to wear the devices on a daily	Professional society guidelines and consensus statements are included in the full report in section 2.3

	Comment	Response
	basis, or in patients who experience significant hypoglycemia.[4] The Association of Children's Diabetes Clinicians, which published a clinical guideline for use of CGM in children diabetes in 2017, emphasized that CGM *with alarms* can be considered for all children on MDI or CSII therapy (Grade A), and should be considered for children of any age with a history of hypoglycemic seizure (Grade B).[37]	
Economic Value of CGM	Although HTCC review considered a number of cost-utility analyses that evaluate the long-term cost-effectiveness of CGM, the review omitted a recently published study that estimated the short-term cost implications of providing CGM to insulin-treated diabetes patients at high risk for costly emergency treatment of severe hypoglycemia.[5] This analysis found that providing CGM to all patients with insulin-treated diabetes who are at high risk for severe hypoglycemia due to hypoglycemia unawareness would result in a 1-year cost savings of $946 to $1346 per patient. This savings is a conservative estimate because it does not account for potential cost savings accrued by reducing the incidence of long-term microvascular and macrovascular complications by lowering HbA1c. Although the ability of CGM to reduce the incidence of severe hypoglycemic has not been well studied, a randomized controlled crossover study by van Beers et al. found that patients with T1D and hypoglycemia unawareness had 59% fewer severe hypoglycemia episodes when using CGM than when using SMBG.[38]	The study by Bronstone is not a full economic study and therefore does not meet inclusion criteria. These data would be valuable, however, for informing a full economic study. The van Beers trial is included in the report
Conclusion	In conclusion, therapeutic CGM is a significant advancement in CGM technology with superior accuracy and demonstrated clinical benefits. We feel the current HTA does not adequately recognize therapeutic CGM as a distinct class of device with unique benefits and has based much of its conclusions on technology that is discontinued and not reflective of current device performance. In contrast, regulatory agencies and payers have recognized that advances in CGM technology provide important benefits to patients and that CGM should be more broadly covered (e.g., therapeutic CGM is now a CMS covered benefit). We urge the technology research	Thank you for your comments. Comments pertaining to formulation of policy do not require a response by the evidence vendor

	Comment	Response
	team to examine the most current evidence, clinical expertise, and Medicare criteria and Medicaid policies when evaluating the strength of evidence for CGM.	
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	Comment	Response
	randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in well-controlled adults with type 1 diabetes. *Diabetes Care* 2017; 40:538-45. 9. Ekhlaspour L, Mondesir D, Lautsch N, Balliro C, Hillard M, Magyar K, et al. Comparative accuracy of 17 point-of-care glucose meters. *J Diabetes Sci Technol* 2017; 11:558-66. 10. Kovatchev BP, Patek SD, Ortiz EA, Breton MD. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. *Diabetes Technol Ther* 2015; 17:177-86. 11. Centers for Medicare and Medicaid Services. Ruling No.: [CMS-1682-R], Classification of therapeutic continuous glucose monitors as "Durable medical equipment" under Medicare Part B. Available at: https://www.cms.gov/regulations-and-guidance/guidance/rulings/cms-rulingsitems/cms1682r.html. Accessed June 26, 2017. 12. CGS Administrators LLC. Glucose Monitors LCD and Related Policy Article – Revised. 2017. Available at: https://www.cgsmedicare.com/jb/pubs/news/2017/05/cope3241.html. Accessed December 4, 2017. 13. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA* 2017; 317:371-78. 14. Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. *Ann Intern Med* 2017; 167:365-74. 15. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin	

	Comment	Response
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	Comment	Response
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Michael Bolen, Director, State Government Affairs, Medtronic		
	Specific comments	

	Comment	Response
Overall Comments, Inclusion of Two Attachements	Good Morning, please see the attached submissions regarding the Washington HTA's re-review of continuous glucose monitors. Since CGM was first approved for children and adolescents in 2011, the technology and utilization of CGM has changed dramatically. Every major commercial health plan in the United States recognizes the clinical and and performance benefits of CGM for high-risk patients with diabetes. We concur with the Objectives described in the Washington HTA Evidence Report developed by Aggregate Analytics. However, we would strongly advise that the Final Report address explicitly the value of CGM for all adults over the age of 18. While it might be implied in the Objectives, it is not specifically stated. At Medtronic, our interest is in diabetes patients' access to CGM used in conjunction with an insulin pump, specifically the MiniMed 670G Hybrid Closed- Loop System. There is now robust evidence concerning the efficacy of this technology for patients who cannot manage their glucose levels with multiple daily injections of insulin. The first attachment is a dossier submitted to New York Medicaid for their review of CGM. Please disregard specific references to New York – the evidence and clinical studies in this document would apply to Washington. The second document provides published and 'real world' data on the 670g System. We appreciate the opportunity to provide you with this information and look forward to HTA's consideration of CGM in January. If you have any questions or concerns, please get in touch Sincerely, Michael Bolen	Thank you for your comments. Comments related to policy do not require a response by the evidence vendor. The report objectives were set *a priori*. The intent of the report was to update a 2011 report and add evidence on CMG use in persons with diabetes in all age groups. This objective has been met. Evaluation/comparisons of insulin delivery methods (with or without CMG) is beyond the scope of this report. We did include trials of CGM that included insulin pumps if they otherwise met our inclusion criteria. We reviewed the dossier and the other attached document provided to assure that studies reported in peer-reviewed publications that met our inclusion criteria had been included in the report.

	Comment	Response
Irl B. Hirsch, MD, Professor of Medicine, University of Washington School of Medicine		
	Specific comments	
General Comments	To whom it may concern: I am a faculty member at the University of Washington and have been the medical director of the Diabetes Care Center since we opened in 1991. I have watched diabetes treatments, both medications and technologies evolve over the decades for both type 1 and type 2 diabetes. For type 1 diabetes, I have seen proliferative retinopathy in this country improve from 50% to under 10% and for diabetic kidney disease, we've seen rates reduced from over 30% to under 5%. And with type 2 diabetes, we've learned how our new diabetes drugs can reduce cardiovascular mortality by over 25-35% over 3 to 5 years. It is always interesting for me to review this recent history with our medical students. Unfortunately, our treatments are far from perfect. While we are doing better than we did 30 years ago, we are not doing as well with the tools we have, and access to both beneficial drugs and technologies continue to be a major public health challenge. I was involved in many of the initial continuous glucose monitoring (CGM) studies over a decade ago, and remained involved today with CGM in general in addition to artificial pancreas work. At both the national and international level, I've been involved in educating physicians how to best use CGM for their patients. Like all new technologies, there were early adopters and the technology was crude by today's standards. But like self-monitoring of blood glucose, this has become the standard of care for many patients. It is important to note that "good diabetes control" should not be limited to HbA1c. A "good" HbA1c below 7% is not "good" if associated with hypoglycemia requiring the assistance of a family member. One problem with many studies is that the only hypoglycemia documented are those episodes requiring paramedic or emergency room visits. We now appreciate that hypoglycemia, often without symptoms after many years of diabetes, can have devastating effects on brain function and cognition.	Thank you for your comments. Comments regarding policy formation or HTCC process are included for transparency but do not require a response from the vendor. RCTs and non-randomized studies (including any from the TD1 Exchange) meeting the inclusion criteria are included in the full report. Studies cited by commenter were included if they met our inclusion criteria. Reasons for exclusion at full text review are included in the appendices. Studies comparing types of insulin delivery were not part of the report scope. With any systematic review, we realize that data may not fully represent the most recent advances and is a "snap shot" that reflects the currently available published evidence from peer –reviewed literature. We have added context to executive summary and background describing changes in devices including accuracy Time spent at hypoglycemic thresholds (and hyperglycemic thresholds), area under the curve and other outcomes are provided in the report as provided by study authors. A summary of time spent in the target range is summarized in the Appendices.

	Comment	Response
	I appreciate that the clinical trials with CGM have been reviewed by your committee. One criticism of diabetes technology trials is actual real-world experience does not reflect clinical trial data. The T1D Exchange is a data registry of American patients with type 1 diabetes of all ages. Currently over 16,000 patients in 76 centers are followed, most of these academic clinics. Overall, use has increased from 7% to 28%. Over a third of adults younger than 65 years-old used CGM, as our oldest population did not have Medicare coverage (this started in the summer of 2017). Note that a quarter of these type 1 patients of Medicare age used this technology, without reimbursement from Medicare. Most of these patients have no awareness to their hypoglycemia. HbA1c (May 2016-July 2017) was lower for each age group using CGM (adjusting for age, duration, race/ethnicity, pump status, income, SMBG, clinic site, $p < 0.001$): In the T1D Exchange, like my clinic at the University of Washington, 60% of patients use insulin pumps. It should be emphasized, however, that the more common insulin delivery outside of our academic centers is with multiple injections, and the T1D Exchange showed improvements with both forms of insulin delivery. Up until now, (at least for the past few years), the only option for multiple injection patients was the Dexcom CGM. In an earlier analysis, the T1D Exchange showed 75% of pump patients used this device. The Dexcom has something that in my mind is under-emphasized to those who are not familiar: the "Share App". This allows family members or friends to be able to watch the CGM data, "real-time" on their smart phones, and be alerted when the blood glucose levels rise too high or drops too low. I have parents use this with their teenage children, and it's even more frequently used for family members of my elderly patients with type 1 diabetes. This is a population that gets minimum visibility in the press, but is growing quickly due to improvements in care for type 1 diabetes. We know from earlier studies in this population average time	

	Comment	Response
	hypoglycemic ranges from 83 to 99 minutes per day (mean age 67 years, mean duration of diabetes 40 years). These patients have minimum awareness to sense their hypoglycemia, which is one reason why Medicare approved CGM in 2017. In fact, our T1D Exchange group also showed that seizure or coma from hypoglycemia occurs in about 20% of patients *per year* after 40 years of diabetes, independent of age when CGM is not used. While we don't have specific randomized controlled trial data for the benefit of reducing hypoglycemic exposure in this older population (or specific trials with the Share App), we are now performing a study called WISDM (Wireless Innovation for Seniors with Diabetes Mellitus) funded by the Helmsley Charitable Trust and the Juvenile Diabetes Research Foundation. Nevertheless, since we now appreciate hypoglycemia unawareness is so profound and dangerous leading to cardiac arrhythmias and death, Medicare agreed it needed to be covered for these patients. While an early study clearly showed that CGM reduced overall diabetes-related complications (Diabetes Care 2010;33:1269-1274), uptake a decade ago was minimal due to the challenges with the early devices, particularly with accuracy. Modern-day CGMs are now quite accurate to the point the FDA has allowed non-adjunctive use (no fingerstick glucose levels to dose insulin) with the Dexcom and Abbott Libre, and a hybrid closed loop with Medtronic. It also needs to be realized that most of the devastating microvascular complications from childhood-onset type 1 diabetes occurs after 10 to 20 years duration of diabetes. In other words, hypoglycemia becomes both the most important clinical aspect of care in addition to the rate-limiting part of insulin treatment. The trajectory of CGM in my adult clinic in Seattle has CGM penetration well over 50% in type 1 diabetes, and in Medicare-age patients I anticipate over 80% within the next year simply to protect from the risks of disabling hypoglycemia.	

	Comment	Response
	One final point: CGM has allowed us to see how poor HbA1c is as a biomarker. We now know that in patients without renal disease, liver disease, or anemia, a HbA1c of 8% could mean the average glucose on CGM could range between 130 and 210 mg/dL. In fact, one person with a HbA1c of 9% could actually have a lower mean glucose than someone else with a HbA1c of 7%! We now understand we all glycate hemoglobin at different rates and hemoglobin has different lifespans in different people. We now teach our students, residents, and fellows to treat the glucose, not the HbA1c as for individual patients, it is often extremely misleading. While treating glucose based on 3 to 4 finger-sticks is certainly better than what we had in the 1960s and 1970s, that doesn't nearly give the granularity required to best dose insulin and minimize hypoglycemia. Thank you in advance for your consideration of covering CGM for all patients who could benefit from this technology. It has revolutionized our ability to care for our patients with diabetes. Please feel free to contact me with any questions. Sincerely, Irl B. Hirsch, MD	
Cate Pihoker, MD, Professor of Pediatrics, University of Washington & Craig Taplin, MD, Associate Professor of Pediatrics, University of Washington		
	Specific comments	
	On behalf of Seattle Children's and the Pediatric Endocrine Division of the Department of Pediatrics, University of Washington, we are responding to the draft report of "Continuous Glucose Monitoring-Update": Below are our key points and references listed below: 1. As clinicians, we have certainly observed that use of CGM has been a huge benefit for children and caregivers. It has led to changes in self-management around timing of insulin, food, and exercise. Such changes in self-management (or caregiver management in the case of younger children) are not often	Thank you for your comments. References provided have been reviewed against the inclusion/exclusion criteria; no additional studies from the list met our inclusion criteria. Meeting abstracts, posters and similar publications do not meet the *a priori* inclusion criteria. We agree that changes in self-management with the use of CGM are not captured in include studies and that studies in children and adolescents employed older devices. We have added context to executive summary and background describing changes in devices

	Comment	Response
	captured in clinical trials. CGM real-time data can now be shared between children, parents and caregivers outside the home (e.g., at school) in real-time. This has led to significant improvements in coordination of care, reduced parental fear of hypoglycemia, and greater collaboration between patients, parents, and schools. 2. There are very few RCT's in youth with CGM and the biggest ones were conducted using older versions of CGM that were significantly less accurate, more painful, and had shorter duration of use. In part because of these factors, patients were less likely to use CGM. Participant use was low, particularly in adolescents, and that low use lead to limited effectiveness. However, even then, consistent CGM use was associated with improvements in glycemic control. Acceptance is much better now, with modern CGM being far more comfortable and accurate, and having a longer sensor life. 3. The report does not specifically address automated insulin delivery such as recent FDA approval and hybrid closed loop therapy (already in wide use clinically). CGM is also intrinsic to hypoglycemia prevention modes such as "low threshold suspend" and "predictive low glucose suspension", both of which are now FDA approved and in wide use by youth. CGM is an essential part of automated insulin delivery. HCL has been clearly demonstrated to decrease rates of nocturnal hypoglycemia and increased time in desired glucose range. Use of CGM and pumps with low threshold suspend has also been associated with reduced hypoglycemia. 4. This report minimizes findings (often by pooling two or more studies) and often reports low evidence 5. Glycemic variability is not emphasized. Reduction of glycemic excursion and time in (desired) range are now key measures in studies assessing diabetes outcomes. 6. Quality of life and fear of hypoglycemia are not emphasized. These are extremely important, as they impact self-management behaviors. Key bodies, such as the JDRF, now	including accuracy and satisfaction. Few trials on newer devices have been published; many older trials are considered pivotal trials and are cited in guidelines and consensus statements relating to the use of CGM. Information on adherence as reported in included trials is included in the full report. Evaluation of insulin delivery systems was not part of the scope for this report. Although data are pooled data for each individual study are provided in the forest plots, results tables and data abstraction allowing for independent evaluation of individual trial data. The intent of pooling data is to summarize them and enhance statistical power to detect differences across trials. Methods used for this systematic review and meta-analysis follow accepted standards (e.g. Cochrane Handbook, AHRQ) Time spent at hypoglycemic thresholds (and hyperglycemic thresholds), area under the curve and other outcomes are provided in the report. Rates of hypoglycemia as reported in the trial are provided in the report. A summary of time spent in the target range is summarized in the Appendices. Guidance on outcomes reporting will hopefully be implemented in future trials. Data from validated measures of quality of life and hypoglycemia fear are included in the full report as secondary measures and detail is provided in data abstraction tables. These were often poorly reported across trials. Findings in most trials did not demonstrate a difference between CGM and SMBG. Guidance for future trials on use of such measures will hopefully be followed.

	Comment	Response
	strongly advocate that we measure care outcomes and overall diabetes control more broadly than just HbA1c, with specific outcomes of value including: variability, quality of life, rates of hypoglycemia, and fear of hypoglycemia. 7. There are additional references that should be considered, including recent international consensus guidelines and a recent abstract presented at ISPAD 2017. 8. Data from recent studies shows the benefits of CGM in exercise in youth. With CGM, youth can more safely participate in vigorous physical activity without severe or recurrent hypoglycemia. CGM has been shown to provide real world guidance on safe management. This guidance is superior to single point in time finger-stick blood glucose measurements in active youth. Critically, closed loop automated insulin delivery has now been shown to maintain glucose time in range and reduce hypoglycemia in exercise settings where frequent blood glucose monitoring is not safe or practical, such as in cold alpine climates, during skiing. These and other studies show clearly that CGM use is associated with safer physical activity in youth with type 1 diabetes, a key driver of better cardiovascular outcomes and quality of life. 9. Data from two observational studies, Type 1 Diabetes Exchange and the DPV, jointly show improvements in A1c with CGM. This is much more striking in 2016 compared to 2011 (see ISPAD abstract). Type 1 Diabetes Exchange, clearly demonstrates improved glycemic control in those using CGM across race/ethnicities. Unfortunately, disparities exist in use of diabetes technologies, including CGM (from Type 1 Exchange and the SEARCH for Diabetes in Youth study). Racial/ethnic minorities and children from lower income families are disproportionately represented by public health insurance plans. We should be working to address these health care disparities, rather than exacerbating them.	

	Comment	Response
	Daniel J. DeSalvo, MOl, Kellee M. Miller, Ph.D., Julia M. Hermann, MS3,4, David M. Maahs, MD, PhDs, Sabine E. Hofer, MD, PhD Mark A. Clements, MD, PhD" Eggert Lilienthal, MD., Jennifer L. Sherr, MO, PhD Martin Tauschmann, MOlO, and Reinhard W. Holl, MD, PhD for the TlD Exchange and DPV registries Title: Continuous Glucose Monitoring (CGM) and Glycemic Control among Youth with Type 1 Diabetes (TlD): International comparison from the TlD Exchange (TlDX) and the DPV Initiative Additional references: Measures of glycemic variability in TlD and the effect of real-time continuous glucose monitoring (El-Laboudi et al Dn, Dec 2017). Targeting postprandial glycemia in children with diabetes: opportunities and challenges (Geyer MC et al Diab Obesity Metab 2017) Practical consideration on the use of CGM in pediatrics and older adults and nonadjunctive use ((Forlenza GP et al Dn 2017) International consensus on use of CGM (Danne T et ai, Diabetes care 2017) Assessing the effectiveness of a 3-month day-and-night home closed-loop control combined with pump suspend feature compared with sensor-augmented pump therapy in youths and adults with suboptimally controlled type 1 diabetes: a randomized parallel study protocol. (Bally Let ai, BMJ Open 2017) Self-monitoring using CGM with real-time feedback improves exercise adherence in individuals with impaired blood glucose: a pilot study. Bailey KJ et ai, Diabetes Technology & Therapeutics, 2016 Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: an observational field study Riddell et ai, Diabetes Technol Ther. 2011 Closed-Loop Control during Intense Prolonged Outdoor Exercise in Adolescents with Type 1	

	Comment	Response
	Diabetes: The Artificial Pancreas Ski Study. Breton MD, Diabetes Care. 2017	
Alyson K Blum, PharmD, CDE, Sacred Heart Center for Maternal Fetal Medicine Diabetes Care Team		
	Specific comments	
	To whom it may concern: I am writing regarding Continuous Glucose Monitor (CGM) coverage for patients with diabetes, before pregnancy and during pregnancy. In 2008, Metzger et al. published the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) Study. This pivotal study has defined glycemic management in pregnancy since its publication. The study concluded that even mild hyperglycemia is toxic to the fetus. Under-treated or poorly controlled diabetes in pregnancy is associated with several adverse pregnancy outcomes including recurrent early pregnancy loss, fetal anomalies (in particular CNS, skeletal and cardiac anomalies), preterm birth, fetal death, preeclampsia, polyhydramnios, IUGR, and macrosomia. Abnormal HbA1c exponentially increases the risk for fetal anomalies. The HAPO study found that an A1c over 10 increased fetal anomaly risk to over 50%. There is an increased incidence of cesarean section and birth trauma. Newborns from diabetic mothers have an increased incidence of delayed lung maturity, neonatal respiratory distress syndrome, jaundice, polycythemia, hypoglycemia, hypothermia, and hypocalcemia. These outcomes can lead to costly NICU admits and prolonged maternal hospital stay. A continuous glucose monitor is the most effective tool for lowering average blood glucose and HbA1c, decreasing time spent hypo- AND hyperglycemic and improving patients safety every day. Multiple studies including the COMISAIR study, the STAR1 and STAR3 studies, a study by Foster et al., the SWITCH study and now the DIaMonD study all show statistically significant improvements in aforementioned outcomes. Including ~30% decrease time in the hypo- and hyperglycemic ranges. Decreased episodes in severe range	Thank you for your comments. Comments regarding policy are included for transparency and do not require a response from the vendor. Suggested references that met the inclusion criteria are summarized in the report. The report includes studies on pregnant women with pre-existing diabetes and gestational diabetes. Trials comparing CGM with SMBG/standard care in these populations were few.

	Comment	Response
	hypoglycemia (<50 mg/dL). Decreased HbA1c by ~1 after 24 weeks. For women who are planning pregnancy, a CGM allows them to have tight control prior to conception. It is not enough to have good control during pregnancy because costly structural fetal anomalies are caused by hyperglycemia during organogenesis before most women even know they are pregnant. If a patient isn't on birth control and is sexually active, they could be pregnant and not know it. For those fetuses, it is too late if they developed sacral agenesis or a cardiac defect because of maternal hyperglycemia. A decrease in A1c of 1 could mean the difference between a healthy baby and a fetal anomaly. Patients with Type 1 Diabetes at the Center for Maternal Fetal Medicine consistently have better maternal and fetal outcomes when they have a CGM. It is imperative these patients keep their BG range under 120 with fasting blood glucose less than 90mg/dL. This level of control inevitably puts the patient at a greater risk for hypoglycemia. CGMs make this control possible and keeps the patient safe and alive. Poor maternal and fetal outcomes associated with uncontrolled diabetes are preventable. Prior to new diabetes technology, infertility plagued women with type 1 diabetes. The incidence of miscarriage was higher as was the incidence of fetal anomalies. However, with pumps and CGMs, patients are able to get pregnant and have a healthy baby. The loss of CGM coverage, for pregnant patients or patients who want to be pregnant, would be devastating. Please feel free to contact us with any additional questions. Respectfully, Alyson K Blum, PharmD, CDE The Center for Maternal Fetal Medicine Diabetes Care Team	
Lawrence T. Smith, President, National Diabetes Volunteer Leadership Council		

	Comment	Response
	Specific comments	
Overall Comments, Request for Consideration of Medicare Coverage Guidelines	Dear Committee Members, I am writing you today on behalf of the National Diabetes Volunteer Leadership Council (NDVLC) to ask for your support for consideration of a rationale coverage determination for Washington State Medicaid recipients for continuous glucose monitoring. This coverage policy would provide access to life saving technology for these patients. Continuous Glucose Monitoring (CGM) for patients with diabetes who use insulin to manage their condition is helping patients better manage their diabetes, which, in turn, reduces the cost burden to the state. Better managed diabetes results in better clinical and economic outcomes. At the American Diabetes Association's Annual Scientific Sessions held this past June (June 8-12, 2017) in San Diego, there were many discussions, symposia and clinical trial results that validated the beneficial impact of CGM on patients with diabetes. CGM is now the Standard of Care for patients using insulin and who are struggling to reach their clinical goals as established by their care teams. The NDVLC would like your consideration for a policy that makes access to the technology reasonable and a process that is not onerous for their care providers. The citizens of Washington State are counting on you for your support so they may have access to a standard of care that is truly lifesaving technology. The Medicare Coverage determination has a good balance for your consideration. According to the framework currently established by CMS, a therapeutic CGM may be covered for any individuals with **Type 1 or Type 2 diabetes on intensive insulin therapy** when all of the following criteria are met: The beneficiary has diabetes mellitus; ***and*** The beneficiary has been using a home blood glucose monitor (BGM) and performing frequent (four or more times a day) BGM testing; ***and***	Thank you for your comments. Comments regarding policy are included for transparency and do not require a response from the vendor. The CMS NCD is included in the report.

	Comment	Response
	The beneficiary is insulin-treated with multiple daily injections (MDI) of insulin or a continuous subcutaneous insulin infusion (CSII) pump; ***and*** The beneficiary's insulin treatment regimen requires frequent adjustment by the beneficiary based on therapeutic CGM testing results. Documentation would be a completed CMN with PA. Please keep in mind that patients on insulin, are at a higher risk for untoward events The membership of the NDVLC is composed of individuals who have previously served in top leadership positions at national voluntary diabetes related health organizations. We are involved in diabetes advocacy on the local, state and national levels on behalf of the 29 million Americans who are living with diabetes. We are asking for your consideration of a coverage policy which balances patient access with making the administrative burden manageable for the healthcare team. Sincerely, Lawrence T. Smith	
Refaat Hegazi, MD, PhD, MS, MPH & Shengsheng Yu, PhD; Abbott Diabetes Care		
	Specific comments	
General Comments	Dear Members of the HTCC, Thank you for accepting public comments on CGM, a revolutionary technology that has seen significant scientific advances in recent years. Although the FreeStyle Libre system was included in the assessment (Table I, Page 20), evidence on its accuracy, clinical outcomes, and economic outcomes was not mentioned in the detailed report/ On behalf of Abbott Diabetes Care, Inc., we are writing to provide scientific support of the clinical and economic effectiveness of a unique, factory-calibrated CGM device, the FreeStyle Libre system, especially given the clear evidence for hypoglycemia reduction and improved adherence to glucose monitoring in adult populations with either Tl or T2 diabetes/ The FreeStyle Libre system is the first and only FDA approved CGM device for adults with diabetes that does not require blood sample calibration	Note: Commenter provided PDFs and cited a number of references (appended to the document following the response tables with original comments) which were reviewed. Full studies published in peer review journals that met our inclusion criteria were included. Meeting abstracts, posters and similar publications do not meet the *a priori* inclusion criteria. Thank you for your comments. This device was approved after our initial search and triage of studies for inclusion, so studies of this did not meet the inclusion criteria at that time. The Bolinder 2016 and Haak 2016 trials have been included in the final report based on very recent approval of the Freestyle Libre device for personal use.

	Comment	Response
	and is indicated to replace blood glucose testing over 10 days of wear, it has been submitted to the Centers for Medicare and Medicaid Services for durable medical equipment coverage under the Part B Medical Benefit, satisfying all requirements as therapeutic CGM.[11] Additional comments related to the inclusion of time in range as one of the primary intermediate outcomes, discontinuation of the FreeStyle Navigator system in the U.S., and the NICE Medtech Innovation Briefing Report on the FreeStyle Libre system arc included in Section III for consideration.	
Clinical Evidence	I. Clinical Evidence and Guidelines of CGM An expert panel of physicians, researchers and individuals experienced in CGM technologies was convened at the AlTO meeting in February 2017 and tasked with developing a consensus statement on CGM use. The International Consensus on the Use of CGM was created and published in the December 20 17 issue of Diabetes Care. This is the latest in a series of expert guidelines regarding the use and effectiveness of CGM.[13] The consensus classified CGM into two main categories: real-time use (rtCGM) and intermittently viewed (iCGM). Given that patients proactively use the FreeStyle Libre reader to read its sensor, the consensus committee referred to the FreeStyle Libre system as iCGM. Following review of the latest clinical evidence, the committee recommended that "CGM should be considered in conjunction with HbAlc for glycemic status assessment and therapy adjustment in all patients with type I diabetes and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia".[13] The committee also recommended, "CGM data should be used to assess hypoglycemia and glucose variability" (p. 1633). II. Clinical and Economic Evidence of the FreeStyle Libre System in Adults with Diabetes Below is a review of the major clinical studies showing the accuracy, effectiveness and safety	Thank you for your comments. Applicable consensus statements from the December Diabetes Care issue have been included in the background section of the report. CMS policy information is included in the report. Meeting abstracts and posters do not meet the inclusion criteria. The Bolinder 2016 and Haak 2016 trials have been included in the final report. Suggested (and attached) references were reviewed against the inclusion criteria for this report.

	Comment	Response
	of the FreeStyle Libre system (FSL) in people with diabetes (PWD).	
Clinical Evidence, Accuracy	1. Accuracy The performance of the FSL system was evaluated in a clinical study conducted at four centers with 48 participants with diabetes (95.8% Type 1, 4.2% Type 2).26 All participants were aged 18 and older. Participants in the study required insulin to manage their diabetes. Each participant wore up to two FSL sensors on the back of the upper arm. During the study, participants tested their blood glucose using fingerstick capillary samples at least eight times during each day of the study. Participants used the blood glucose meter built into the FSL reader. Additionally, venous blood glucose was analyzed up to 128 times over four separate visits to the clinical center. Venous blood was analyzed using the Yellow Springs Instrument Life Sciences 2300 STAT Plus™ Glucose & Lactate Analyzer (YSI). YSI is a laboratory glucose and lactate analyzer of whole blood and plasma and is a widely recognized standard in laboratory analysis of blood glucose. Glucose readings obtained from the system were compared to glucose readings obtained from the YSI to evaluate the performance of the system. Three lots of sensors were evaluated in the study. Agreement between FreeStyle Libre glucose measurement and YSI reading of venous blood glucose was used to evaluate the accuracy of CGM versus YSI reference. Overall, 91.1% of results were within ±20 mg/dL /120% of YSI reference. The overall accuracy was also measured by comparing the Mean and Median Absolute Relative Difference between the FSL and reference YSI glucose values. The Mean or Median Absolute Relative Difference gives an indication of the average percent disagreement between the CGM and the reference. Based on the 5,772-paired readings, the Mean Absolute Relative Difference was 9.7% for the comparison with YSI reference. The Median Absolute Relative Difference shows that half of the time the system was within 7.7% of the YSI reference. Agreement between the FSL and capillary blood glucose values (8G) as measured by the reader's built-in meter was characterized by using paired FreeStyle Libre glucose measurement and BG value. Overall,	Thank you for your comments. Information from the trials published in peer-reviewed journals that met the inclusion criteria and the FDA SSED for this device are included in the report.

	Comment	Response
	84.3% of results were within ±20 mg/dL/ 120% of SG values. Based on 3,680-paired readings, the Mean Absolute Relative Difference was 12.1% for the comparison with BG value. The Median Absolute Relative Difference showed half of the time the system was within 9.4% of the SG value. No device related serious adverse events occurred during the study. Mild skin irritations, such as erythema, edema, rash, bleeding, itching, induration, and infection were reported around the insertion site and adhesive area by a moderate frequency of participants (5 out of 48 or 10.4%). Pain was mostly reported as none, with only one instance of mild pain. For more information regarding the accuracy of the FreeStyle Libre system, please refer to the user's manual available at: https://freestyleserver.com/PayloadsIlFU/20 17 sep/ART3 8SS3-OOI _rev-C-Web. Pdf	
Clinical Evidence, Efficacy and Safety	a. In Adults with TlDM The IMPACT trial was a randomized study comparing the FSL system with the current standard of care (self-monitoring of blood glucose, 5MBG) in people with Tl DM9. Patients were enrolled from 23 European diabetes centers. The primary outcome of the study was change in time in hypoglycemia (<70 mg/dL) between baseline and 6 months. After the screening and baseline phase, 120 participants were randomly assigned to the intervention group and 121 to the control group, with outcomes being evaluated in 119 and 120, respectively. Mean time in hypoglycemia changed from 3.38 h/day at baseline to 2.03 h/day at 6 months (baseline adjusted mean change - 1.39) in the intervention group, and from 3.44 h/day to 3.27 h/day in the control group (- 0. 14); with the between-group difference of -1.24 (SE 0.239; p<0.0001), equating to a 38% reduction in time in hypoglycemia in the intervention group. The reduction in hypoglycemia exposure (time and events) was similar during both daytime and nighttime, and the pattern of daily scanning showed that the highest frequency occurred in the evening, indicating patients most likely took the necessary adjustments to their insulin or carbohydrate intake before sleep. There were also significant between-group differences	The trials by Bolinder and Haak been included in the final report. Meeting abstracts, proceedings or posters do not meet inclusion criteria.

	Comment	Response
	favoring the intervention group compared with the control group in the glycemic variability measures. The mean number of self-monitored blood glucose tests performed per day by the intervention group immediately reduced from 5.5 (SD 2.0) tests per day in the 14-day baseline phase to 0.5 (0.7) test per day during the treatment phase of the trial. This was an unprompted response by intervention participants that clinically equates to approximately one self-monitoring blood glucose test every 2 days. The mean number of sensor scans per day for the intervention group was 15.1 (SD 6.9) during the treatment phase. Importantly, assessing patient reported outcomes showed that patient satisfaction with treatment was significantly improved for intervention compared with control (adjusted between-group difference - 0.24 [SE 0.049]; p<O.OOO I). The total treatment satisfaction and perceived frequency of hyperglycemia were also significantly improved in the intervention group compared with the control group. No device-related hypoglycemia or safety issues were reported. There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device. It can be concluded from the IMPACT study that the FSL system safely reduced the time adults with well-controlled type I diabetes spent in hypoglycemia, decreased glycemic variability, increased time in range and improved key patient reported outcomes. b. In Adults with T2DM FSL has been also studied in people with TIDI7. ln an open-label, randomized controlled study (REPLACE), adults with type 2 diabetes, on intensive insulin therapy from 26 European diabetes centers, were enrolled. Following 2 weeks of blinded sensor wear, 2: 1 (intervention/control) randomization was to intervention (FSL) or control (SMBG). Primary outcome was difference in HbA1c at 6 months in the full analysis set. Prespecified secondary outcomes included time in hypoglycemia, effect of age, and patient satisfaction. Participants (n = 224) were randomized into the two groups (149 intervention, 75 controls). At 6 months, while there was no difference in the change in HbA1c	

	Comment	Response
	between intervention and controls (-0.29 ± 0.07% [mean ± SE] and - 0.31 ± 0.09%, respectively; p = 0.8222), a difference was detected in favor of FSL in participants aged <65 years (-0.53 ± 0.09% and -0.20 ± 0. 12%, respectively; p = 0.030 I). Time in hypoglycemia <70 mg/dL reduced by 0.47 ± 0. 13 h/day (mean ± SE; P ~ 0.0006), and <55 mg/dL reduced by 0.22 ± 0.07 h/day (p = 0.0014) for intervention participants compared with controls, equating to reductions of 43% and 53%, respectively. 5MBG frequency, similar at baseline, decreased in intervention participants from 3.8 ± 1.4 tests/day (mean ± SO) to 0.3 ± 0.7, and remained unchanged in controls (average of 3.9 ± 1.5 test/day at baseline and 3.8 ± 1.9 at the end of the study). The mean number of sensor scans per day for the intervention group was 8.3 (SD 4.4) during the treatment phase. Treatment satisfaction was higher in intervention compared with controls (DTSQ 13.1 ± 0.50 [mean ± SE] and 9.0 ± 0.72, respectively; p < 0.0001). No serious adverse events or severe hypoglycemic events were reported related to sensor data use. In summary, the REPLACE study demonstrated that the use of FSL in type 2 diabetes treated with intensive insulin therapy resulted in no difference in HbA1c change but did reduce hypoglycemia, thus offering a safe and effective replacement for SMBG. In a 12-month follow-up of 139 patients, enrolled in the REPLACE trial and having completed the 6-month treatment phase who continued into the open-access phase for an additional 6 months, time in hypoglycemia (sensor glucose 70 mg/dL) was reduced by 50% compared to baseline (-0.70 ± 1.85/24 h [mean ± standard deviation] ~ p = 0.0002) at 12 months.[18] Nocturnal hypoglycemia (2300 to 0600 hours, <70 mg/dL) was reduced by 52%; P ~ 0.0002. There was no change in time in range (sensor glucose 70-180 mg/dL). 5MBG testing fell from a mean of 3.9 (median 3.9) times/day at baseline to 0.2 (0.0), with an average frequency of sensor scanning of 7.1 (5.7) times/day at 12 months. During this 6-month extension period, no device-related serious adverse events were reported. Nine participants	

	Comment	Response
	reported 16 instances of device-related adverse events (e.g. infect ion, allergy). This follow up cohort demonstrates that the use of FSL for glycemic management in individuals with type 2 diabetes treated with intensive insulin therapy over 12 months was associated with a sustained reduction in hypoglycemia and safely and effectively replaced SMBG.	
Real World Evidence	De-identified data from all FSL users willing to participate were included in a real-world database. When connected to the computer-based software with an active internet connection, the FSL reader's 90-day memory was de-identified and uploaded to the database. The aim was to evaluate association of real-world scanning with the FreeStyle Libre system and glucose control measures. For analysis, sensors were required to have at least 120 hours of use. From September 2014 to May 2016, data were collected from 50,831 readers with 279,446 sensors, comprising a total of 86.4 million monitoring hours (63.8 million scans). Twenty equally-sized groups were created based on lowest to highest rate of scanning (n = 2542 each). Six regions were identified, the five countries having the highest device use (Germany, Spain, France, UK and Italy), and a sixth "region" grouped all remaining countries. Scan rate per reader was determined and twenty equally-sized rank-ordered groups, categorized by scan frequency, were evaluated. Glucose scan frequency was analyzed together with relationship to glycemic markers in each of these regions. These analyses were reported at AlTD, ADA and EASD in 20171.1 4.15. Real-world users of the FreeStyle Libre system scanned at a high frequency. The users performed a mean of 16.3 scans per day (median, 14; interquartile range, 10-20), with a mean of 1.6 scans per day between midnight and 6 AM. These data show that people using the FreeStyle Libre system typically monitor their glucose at a frequency that meets or exceeds that recommended by guidelines2.24, a much higher rate than that typically achieved using SMBG. The high scanning frequency in the database is similar to the frequency observed in the IMPACT trial, demonstrating the high level of acceptance of the device by patients in a	Thank you. Meeting abstracts, proceedings or posters do not meet inclusion criteria.

	Comment	Response
	real-world setting. SMBG testing was low, with a median of 0.36 tests per day via the built-in meter, confirming the IMPACT trial finding that people did not feel the need to routinely supplement their glucose monitoring via the FreeStyle Libre system with additional SMBG. Additionally, the higher rates of scanning were significantly associated with improved glucose control. As scan rate increased from the lowest group (mean 4.4 scans per day) to the highest (mean 48.1 scans pcr day), the time spent in the target glycemic range (70-180 mg/dL) increased from 12.0 to 16.8 hours per day (40% increase; $p < 0.001$), and time spent in hyperglycemia (≥180 mg/dL) decreased by 44%, from a mean (SD) of 10.5 ± 5 to 5.9 ± 5 hours per day ($p<0.001$). The duration of time spent in hypoglycemia reduced significantly, with greater reductions seen in more severe hypoglycemic states: time below 70, 55, and 45 mg/dL decreased by 15%, 40%, and 49% respectively (all $p< 0.001$). All metrics were improved for individuals scanning at the median frequency (14 scans per day), compared with the lowest-scanning group. Estimated HbA1c in the highest scanning frequency group was significantly lower than in the group that scanned least frequently (6.7% vs 8.0%; $p < 0.001$), and there was a consistent trend towards lower estimated HbA1c as scanning frequency increased. Average scan frequency varied significantly across regions: the highest mean scan frequency was in the UK, where participants scanned a mean of 18.0 (median, 15; IQR, 11- 23) times per day and the lowest scan frequency in France, at 13.6 (median, 12; IQR, 8- 17) scans per day. Participants in France spent the longest time in hypoglycemia, with a mean (± SD) of 58 (± 65) to 40 (± 62) minutes per day with glucose < 55 mg/dL in the lowest and highest frequency scanning groups, respectively. Individuals from Italy spent the least amount of time in hypoglycemia, with a mean (± SD) of 33 (± 59) to 20 (± 35) minutes per day with glucose < 55 mg/dL in the lowest and highest frequency scanning groups, respectively. The real-world database represents an extremely large population utilizing the	

	Comment	Response
	FreeStyle Libre system, which allows detailed assessment of measures of hyperglycemia, hypoglycemia, and self-monitoring behaviors. Limitations of the database include a lack of specific demographic data, precluding precise conclusions regarding users with type 1 or type 2 diabetes. The database also does not include data on glucose control before participants started using the FreeStyle Libre system, and conclusions about the impact of initiating system use cannot be made.	
Cost-Effectiveness Analysis	The FSL system was launched in Europe in 2014 and Canada in the summer of 2017. Following FDA approval in September 2017, the FSL system was launched in the US in November. The assessment of cost-effectiveness of the FSL system has been based on the IQVIA Core Diabetes Model (CDM)". (IQVIA were formerly known as IMS). The COM has been used for both T1 and 1'2 MDI populations by pharmaceutical and medical device manufacturers, including other COM manufacturers. COM has been used to demonstrate the cost-effectiveness of the FSL system compared with SMBG in various European countries and Australia, based on inputs from the IMPACT and REPLACE RCTs. The T and T2 versions of COM for the FSL also include a health utility increment (0.03) for the FSL compared with SMBG that was obtained from a time trade-off study 22. This study quantified the preference of a general population for using a factory calibrated COM, such as the FSL system to monitor glucose levels as an alternative to SMBG. Enclosed are posters presented at ISPOR (Boston, USA 2017) demonstrating the cost-effectiveness of the FSL in T1 and T2 MDI, based on the CDM from the perspective of the UK National Health Service (NHS). [6,27] The base case for Tl MDI shows an lCER of $33,810/QALY (GBP 25,045 assuming an exchange rate of $1.35 to a British pound) and the base case for T2 MDl shows an ICER of$32,187/QALY (OBP 23,842). These base case results were supported by various scenarios, hence it was concluded that the FSL system is cost-effective for both TI and T2 MDI populations based on a typical UK willingness-	Thank you for your comments. Meeting abstracts, proceedings or posters do not meet inclusion criteria.

	Comment	Response
	to-pay threshold of about OBP 30,000/QALY. The findings from the UK base case and scenarios are supported by the COM produced for Sweden that was presented at ISPOR (Vienna, Austria 2016). These posters also included base case results from Germany, Italy, France, Netherlands, and Australia. [5,21] These results support the conclusion that the FSL system is cost-effective across a range of health systems for both T1 and T2 MDl populations. Additional exploratory evidence for the cost-effecti veness of the FSL system in T1 and T2 MDI from a Swedish perspective was recently presented at ISPOR (Glasgow, 2017), although this time incorporating the real -world evidence from over 50,000 readers.[14] These models show that the reductions in HbA1c and hypoglycemia that are associated with the increased frequency of glucose monitoring observed in the real world for FSL compared with 5MBG support the cost-effectiveness of the FSL.[7,8] The posters for these various COM presentations are enclosed. Manuscripts are being submitted to journals in early 2018 for publication. There are various limitations of the cost-effectiveness models for the FSL, although these are similar to the limitations noted for the models for other CGM devices in the draft evidence report. The REPLACE and IMPACT studies were 6 months in duration, the models are not based on American healthcare inputs, and the manufacturer sponsors them. However, the ICERs provided for the FSL system for the T1 MDI population are below the lower end of the range provided by the previous studies of CGM devices. For the T2 MDI population, the ICER for the FSL system is of similar magnitude to that obtained for the T I MDI population. Note that although this ICER for a T2 MDI population is greater than that from the only other T2 cost-effectiveness study of a COM device in the draft evidence report, the model for the FSL was based on continuous use of the device whereas the other study was based on intermittent use. The limitations of the FSL cost-effectiveness models should also be considered alongside several reasons why the ICERs for the FSL system could be considered conservative,	

	Comment	Response
	especially when compared with previous studies of COM devices included in the draft evidence report: **Diminishing Disutility for Hypoglycemia Events compared with Fixed Disutility per Event:** Previous assessments of CGM devices[10] typically assumed a fixed disutility per nonsevere hypoglycemic event (NSHE). Recent literature has shown disutility per NSHE declines with increased rates of NSHE[20], and so the average disutility per event is lower than that assumed for the earlier method.[4,12] All other things being equal, the more recent diminishing marginal disutility method as used for the FSL COM, will tend to produce much higher ICER values than the fixed disutility method used in previous assessments. For reference, scenario 11 in Table 3 and Figure 1 of the UK NHS poster for Tl MDI shows this assumption makes a large difference to the ICER. **No Difference in Severe Hypoglycemia Events assumed in Base Case for FSL COM:** The base case for the FSL COM assumed no difference in severe hypoglycemia events (SHE) compared with 5MBG, but the IMPACT and REPLACE studies showed a substantial reduction in hypoglycemic events less than 40mg/dl in favor of the FSL (55% in IMPACT, 48% in REPLACE). There is likely to be a large reduction in SHEs for the FSL that is similar to that assumed for other CGMs.[10] For example, assuming a 55% reduction in SHEs, based on events less than 40mg/dl from the IMPACT study as a proxy, the ICER for FSL in T1 MDI for UK NHS (provided above) reduces from $33,810/QALY to $14,935/QALY (for reference see scenario 9 in Table 3 and Figure 1 of the UK NHS poster for T2 MDI). **Link between Severe Hypoglycemia and Cardiovascular Events not included in T2** **CDM:** Evidence from a meta-analysis has shown that patients with T2DM who experience severe hypoglycemia may be at an increased risk of cardiovascular events 16 This effect is not incorporated in the lQVIA CDM. Potentially the lCER for the FSL system may be higher than it would be if the CDM accounted for the	

	Comment	Response
	associated CV events connected with hypoglycemia observed in the REPLACE study for patients using the FSL compared with those using routine SMBG. These factors need to be considered alongside the limitations of the FSL cost-effectiveness models since potentially the lCERs for the FSL system are conservative, especially when compared with the previous studies of CGM devices. In conclusion, based on evidence from seven countries, Abbott Diabetes Care believes the FreeStyle Libre system is of at least the same economic value as the CGM devices assessed previously in the population of T1 and T2 patients using MDI. For the reasons provided in the bullet points above, the FreeStyle Libre system may be of even greater economic value than the other CGM devices. **Key Assumptions used in CDM for the FSL compared with CDM for Dexcom G5** As mentioned above, the CDM has been used by other CGM manufacturers. There are similarities between the version of CDM used for Dexcom G5 in a Tl population for Canada[10] and the version used for the FSL in Canada and European countries, but there are some important differences that are provided in the table below (Canadian costs are provided as an example): The assumptions used for the Dexcom GS COM concerning (1) the reduction in rate of severe hypoglycemia events, (2) the costs of severe and non-severe hypoglycemia events, and (3) the disutility associated with non-severe hypoglycemia events, are all more aggressive than the corresponding assumptions used for the FSL COM. The Dexcom GS COM cannot claim the utility increment (0.03) compared with routine 5MBG that has been published for the FSL system, because daily SMBG is required to calibrate the GS system. The table also shows the cost of the GS system is much higher than the FSL system in Canada, and the same is true for the US based on list prices. Dexcom report a cost of $4S3 .68 per 9-month transmitter, $793.80 per receiver (1-year warranty) and $566.69 per box of four sensors, which is one month's supply. These values imply an aggregate cost of $8,200 PPPY for the system, on top of which must be added the cost of daily	

	Comment	Response
	SMBG to calibrate the system (2.3 tests/day). In contrast, the FSL system costs $36 per 10-day sensor and the reader is free of charge, which implies a cost of $1,314 PPPY for the system (i.e. 36.S sensors PPPY). The cost of occasional 5MBG to confirm readings in certain specific situations for the FSL system (O.S tests/day) will be less than the 5MBG for daily calibration required by the GS system. In summary, the cost of the FreeStyle Libre system is substantially less PPPY than the GS system ($6,886 less on a PPPY basis) and the cost per QALY is less than for the GS system, especially once the more aggressive assumptions used for the GS COM are considered. Based on these findings, Abbott Diabetes Care believes the FSL system to be more affordable and of greater economic value than the GS system in T1 and T2 patients using MDI. Evidence to support the affordability of the FSL system in Tl MDI based on UK NHS costs was presented at ADA (San Diego, 2017)[19] and for T2 MDI based on German costs was presented at ISPOR (Vienna, 2016)[29] The cost calculation for Tl MDI population in UK shows that the FSL was associated with a small increase in acquisition costs with a potential for overall cost savings related to a reduction in severe hypoglycemia events compared with SMBG. For the T2 MDI population in Germany, the cost calculation shows that the FSL was associated with an increase in acquisition cost compared with SMBG that was offset by a reduction in costs of hospitalization and the use of emergency rooms and ambulances. The posters for these cost calculations are enclosed.	
Comments on Primary Intermediate Outcomes, FreeStyle Navigator, and NICE Medtech Innovation Briefing Report on the FreeStyle Libre System[25]	We would like to recommend time in range as one of the primary intermediate outcomes for assessment. Frequent and appropriate measurements of glucose control are crucial for optimal diabetes management. HbAlc has been the gold standard for setting treatment target and predicting risk for developing long-term complications. Given the clinical adoption of CGM technology, there is increased knowledge on the limitation of HbA1c, and new metrics have been proposed to better understand the dynamic nature of glucose control, and help	Thank you for your comments. When reported in included studies, time spent in various glycemic ranges is reported as described the authors of the studies. Time in target range was poorly reported across trials; Data available from included studies in included in the appendices.

	Comment	Response
	patient achieve optimal control and reduce diabetes related complications. Among the metrics derived from CGM technology, time in range, expressed either as "% of glucose readings" or "hours per day" with the proposed target range of 70-180 mg/dL, has been consensually recognized and recommended by the clinical and scientific community.[3,28] We would also like to mention that since 20 11 , FreeStyle Navigator is no longer commercially available in the United States. Based on the major differences in product feature and performance between the FreeStyle Navigator and the FreeStyle Libre systems, we will leave the discretion to the reviewers whether or not the FreeStyle Navigator system should still be included in this report. In addition to the NICE guidelines on integrated sensor-augmented pump therapy and diabetes diagnosis and management for type I diabetes on pages 26-28, we would like to supply the NICE Medtech Innovation Briefing on the FreeStyle Libre for Glucose Monitoring, published on July 3 20 17.[25] The report recognizes the FreeStyle Libre system "as an alternative to routine blood glucose monitoring in people with type 1 and 2 diabetes who use insulin injections."	Three trials of traditional CGM in persons with T1D using more current devices were included in the DRAFT report (Beck 2017, Lind 2017, van Beers 2016) in addition to the Bolinder and Haak trials of the Libre device. If these would be the only trials considered, evidence would be limited. Many of the older included trials are considered pivotal trials and are cited in guidelines. References cited in the letter and the NICE briefing were reviewed; articles meeting our inclusion criteria were included in the report.
Conclusion	In addition to the NICE guidelines on integrated sensor-augmented pump therapy and diabetes diagnosis and management for type I diabetes on pages 26-28, we would like to supply the NICE Medtech Innovation Briefing on the FreeStyle Libre for Glucose Monitoring, published on July 3 2017.[25] The report recognizes the FreeStyle Libre system "as an alternative to routine blood glucose monitoring in people with type 1 and 2 diabetes who use insulin injections." In conclusion, the use of COM is a game-changer in the management of PWD. This revolutionary technology provides an affordable and cost-effective solution to enable PWD to gain breadth of knowledge of their glycemic measures beyond hyperglycemia, namely hypoglycemia and glycemic variability. The use of the FSL has been proven to reduce time in hypoglycemia in patients with both T1D and T2D, significantly reduce the need for SMBG and improve certain patient reported	References cited in the letter and the NICE briefing were reviewed; articles meeting our inclusion criteria were included.

	Comment	Response
	outcomes, importantly diabetes treatment satisfaction. **References** I. Ajjan RA, Xu Y. Hayter G, Dunn T. Flash glucose monitoring in over 50,000 users: a favourable relationship between frequency of testing and glycaemic measures. *Diabetologia* 2017 Sep I; 60, S329-S329. 2. American Diabetes Association. Standards of medical care in diabetes - 20 17. *Diabetes Care,* 2017 January I; 40(Supp.I). 3. Agiostratidou G, Anhalt H, Ball 0 , Blonde L, Gourgari E, Harriman KN, Kowalski AJ, Madden P, MCAuliffe-Fogarty AH, McElwee-Malloy M, Peters A. Standardizing Clinically Meaningful Outcome Measures Beyond HbAlc for Type I Diabetes: A Consensus Report of the American Associat ion of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, lDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the TI D Exchange. *Diabeles Care,* 2017 Dec; 1;40(12):1622-30. 4. Beaudet A, Clegg *I ,* Thuresson PO, Lioyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. *Value in Health,* 2014;17(4), 462-470. 5. Bilir SP, Li H, Wehler EA, Hellmund R, Munakata J. Cost effect iveness analysis ofa flash glucose monitoring system for type I diabetes (T I OM) patients receiving intensive insulin treatment in Europe and Australi a. *Value in Health,* 2016 Nov I; 19(7):A697-8. Presented at ISPOR-EU International Society for hannacoeconomics and Outcomes Research - 19th Annual European Congress, Oct 29, 2016, Vienna, Austri a. (20 16). Poster attached. 6. Bilir, SP, Li 1-1, Wehler S, Hellmund R, Munakata J. Cost effectiveness analysis of a flash continuous glucose monitoring system for type 1 diabetes (T I DM) patients	

	Comment	Response
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	Comment	Response
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	Comment	Response
	diagnosis and management [NG 17]. August 20 15. Available from : https:l/www.nice.org.uklguidance/ng I7 (Accessed Deccmber 7, 2017). 25. NICE Medtech Innovation Briefing on FreeStyle Libre for Glucose Monitoring, published on July 3 2017. Available at: https:llwww.nice.org.ukladvice/mibIIO 26. PMA P1 5002 1: FDA Summary of Safety and Effectiveness Data, pp. 17-27. https:llwww.accessdata.fda.gov/cdrh_docsl pdn51P15002 IB.pdf 27. Wehler B, Li H, Bilir SP, Hellmund R, Munakata J. Cost effectiveness analysis of a flash continuous glucose monitoring system for type 2 diabetes (T2DM) patients receiving intensive insulin treatment in the UK. Presented at ISPOR- International Society for Pharmacoeconomics and Outcomes Research 22nd Annual International Congress, Boston MA (2017, May). Poster attached. 28. Wright LAC, Hirsch lB. Metrics beyond hemoglobin Ale in diabetes management: time in range. hypoglycemia and other parameters. DiabetesTechnology & Therapeutics, 2017; 19(52), S- 16. 29. Hellmund R. Budget impact analysis ofa nash glucose monitoring system for people with type 2 diabetes who are using intensive insulin [Poster]. Presented at the International Society for Pharmacoeconomics and Outcomes Research 19th Annual European Congress, 29 October- 2 November 20 16, Vienna, Austria. Poster attached.	
Lindsey De Koster		
	Specific comments	
	To Whom it may concern: I KNOW THIS IS LENGTHY BUT PLEASE, PLEASE READ. I am a 31-year-old female who was diagnosed with Type I diabetes about 11 months ago. The	Thank you for your comments.

	Comment	Response
	diagnosis has been life changing for me. I have had a difficult time with controlling my blood sugars. I seem to fluctuate up and down easily and I don't always have the ability to poke my finger and check my BG as often as is necessary to check where I am at with these significant BG level swings. I have been told through diabetes education that I will learn to "feel" when I am going high or low. Unfortunately I "feel" better at 250-300 and I "feel" low when I am at 175. I have anxiety problems and the fear of going low makes me very anxious. I have experienced too many times my BG going as low as 20 and I have drank two juice boxes, candy, peanut butter and jelly sandwich + more and it took over one hour to get BG level to 50 and over another hour to get over 100. This is very difficult to negotiate when it happens at work. Molina approved paying for blood glucose monitoring system and Dexcom sent me the device and then when it was time to put an order in for new supplies I was told that Molina would no longer cover this blood glucose monitoring system. I have used the continuous blood monitoring system for two weeks and it has been helping me to understand my diabetes better because I am able to see my BG levels every 5 minutes and I can get alarms before my sugars get high or begin to go lower. The fear and anxiety I have had has decreased greatly. THIS DEVICE MAKES ME FEEL HOPEFUL IN THAT I WILL BE MORE SUCCESSFUL DEALING WITH THIS LIFE LONG, SERIOUS, INCURABLE DISEASE AND THE RESULTS OF COMPLICATIONS OF DIABETES LIKE HEART DISEASE, EYE SIGHT, KIDNEY ISSUES, CIRCULATION, NUMBNESS ETC. I do not understand why Medicaid would not want to pay for something that would help with preventing or at least diminish the complications that come with having diabetes. Diabetes will dictate every aspect of my life, every single day for the rest of my life. If I cannot convince you with the above comments that the continuous blood monitoring system can help me 24 hours a day to negotiate the diabetes and the complications of diabetes then maybe I can appeal to your sensibilities that covering the continuous blood glucose monitoring system would be	

	Comment	Response
	advantageous to Molina and financially prudent to Molina. In the last 11 months I have been hospitalized at least 3 x with DKA and about 2 x going to ER and received DKA protocol treatment and was able to be released without being admitted. I have lost 60 pounds in 11 months and I am now 115 pounds. I really cannot lose too much more weight. This is directly attributed to poor blood sugar control. I know the continuous blood sugar monitoring system is not a "miracle" device. But I am convinced that using this device will be an important part in helping my success with understanding my diabetes. The device gives me the ability I to make small adjustments with my blood glucose levels vs going high and then try to make big insulin adjustments only to go too low and then having to adjust with food and so the cycle goes. With being able to see my BG level every 5 minutes I am confident that in 6 months my AC 1 numbers will improve. Please consider covering this device. It gives me hope and some peace that this device is my helper. Sincerely, Lindsey De Koster	

APPENDIX: Clinical/peer reviews and public comments received

CLINICAL/PEER REVIEW # 1: Jessica Castle, MD

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **Continuous Glucose Monitoring Re-review Report** Your contribution and time are greatly appreciated.

The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

The report and appendices are available at: https://www.hca.wa.gov/about-hca/health-technology-assessment/glucose-monitoring

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to focus on the substance/content of the report.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: andrea@aggregate-analytics.com

I will need your review by Friday, December 1, 2017 at the latest.

If you have questions or concerns please contact andrea@aggregate-analytics.com. Thanks!

Reviewer Identification Information

Reviewer Name	**Jessica Castle, MD**
Address	**Street 11523 SW 27th Ave** **City Portland** **State Oregon** **Zip Code 97219**
Phone	**503-494-7072**
E-mail	**castleje@ohsu.edu**

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

Page ES-1 Line

The topic is appropriate and the public policy and clinical relevance is well defined. It should be made evident that this review does not cover automated insulin delivery, which is an important but separate topic relating to CGM.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Page ES-1 Line

The paragraph implies that other autoimmune disorders are a complication of diabetes, whereas having one autoimmune disease (such as type 1 diabetes) increases your genetic risk of having a second autoimmune disease.

Page ES-1 Line

As is mentioned in the document, CGM measures interstitial glucose, so it is more accurate to state it displays the current glucose level (not current blood glucose level, as it does not measure blood glucose). Please remove references to blood glucose in relation to CGM.

Page ES-2 Line

In terms of outcomes, recommend considering time in hypoglycemia and severe hypoglycemia separately.

Page 13 Line

Under background, it should be noted that not all patients with type 2 diabetes end up on insulin. Gestational diabetes should be defined separately from diabetes in pregnancy.

Page 16 Line

An A1C of 5.7% or higher is abnormal (not 6%).

Page 17 Line

Please provider a reference for the comment that a measurement of glucose by the CGM takes 7-15 minutes before it is displayed. I don't believe that is accurate. There is a physiological delay as the report notes, and CGM values in the past were smoothed which imparted a delay (but I believe this smoothing has been removed/minimized with current day devices).

The report reads “the FDA has not approved any CGM device for insulin dosing decisions, so persons using CGM must still conduct SMBG several times a day.” The Dexcom G5 is approved for non-adjunctive use and the Medtronic 670G system automates insulin delivery based on CGM.

Please add a discussion in the executive summary and in the background section on the changing accuracy of CGM from 2011 to now. CGM has changed significantly since 2011 (in terms of user experience and accuracy) and a reader should be aware of that when reading this report. Consider, for example, the average CGM wear time from the landmark 2008 NEJM JDRF trial as compared to the DIAMOND trial.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

Page Line

Yes, aims and objectives clearly address relevant policy and clinical issues and key questions were clearly defined and adequate for achieving aims.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Page 64 Line

I think it is useful to consider all available data for CGM, but as described above, making conclusions about current day CGM based on older data, including data from 2008-2012, is problematic.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

Page ES-6 Line

The difficulty with reviewing data from 2011-2017 with regards to CGM is that CGM has so drastically changed over this time period with marked improvement and usability. I suggest naming the devices used in the results section as outcomes with the use of an older device, as well as user experience with regards to alarms, usability of the device, and discontinuation rates, may not apply to a newer device given differences in accuracy, ability to share data, and other features.

Page ES-6 *Page* Line

Macrovascular complications and fetal outcomes don't really apply to children, so I think those should be removed in the table of ≤18 years of age or notate as no evidence/not applicable.

Page ES-7 Line

In the result table starting on page ES-6, time in hypoglycemia should be considered separately from severe hypoglycemia. The latter occurs much less frequently, and studies are often not powered to detect a difference for this less frequent event. The field is coming to a consensus that time <70 mg/dL should also be considered separately from <54 mg/dL, although those metrics are not available from many past studies.

Page ES-9 Line

Severe hypoglycemia is defined by the American Diabetes Association as requiring assistance from another individual. So I would not use that term for < 55 mg/dL. In a recent consensus paper (reference below), glucose <54 mg/dL was defined as Level 2 hypoglycemia. Discussion of hypoglycemia throughout the document needs to be revised to be clear on percentage of time <54 mg/dL and episodes of severe hypoglycemia (such as a hypoglycemic seizure), as these are two different outcomes.

It would be useful to reference which study is being described in the summary of results in the event a reader wants to find more information. A simple number reference corresponding to the reference listed at the end would suffice.

Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, Kowalski AJ, Madden P, McAuliffe-Fogarty AH, McElwee-Malloy M, Peters A. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017 Dec 1;40(12):1622-30.

Page ES-14 Line

The report reads "Adults with type 1 DM not taking prandial insulin." Should this read type 2 DM?

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Page 158 Line

At the beginning of table 5.1.1, CGM is labeled GCM, which may confuse readers.

Page 158 Line

It would be worthwhile to highlight the conclusions based on recent data (for example only studies using Dexcom G4 with software 505 algorithm, G5, Enlite or Guardian 3). As noted above, data published in 2008 likely does not reflect results obtained with current day sensors.

Page 160 Line

As noted above, severe hypoglycemia is defined as requiring assistance from a third party, not a glucose of 55 or less.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

Page Line

I have no concerns about the overall presentation and the topic is very relevant to clinical medicine and public policy/public health.

QUALITY OF REPORT

Quality Of the Report
(Click in the gray box to make your selection)

Superior

Good X

Fair

Poor

CLINICAL/PEER REVIEW # 2: Ines Guttmann – Bauman, MD

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **Continuous Glucose Monitoring Re-review Report** Your contribution and time are greatly appreciated.

The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

The report and appendices are available at: https://www.hca.wa.gov/about-hca/health-technology-assessment/glucose-monitoring

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to focus on the substance/content of the report.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: andrea@aggregate-analytics.com

I will need your review by Friday, December 1, 2017 at the latest.

If you have questions or concerns please contact andrea@aggregate-analytics.com. Thanks!

Reviewer Identification Information

Reviewer Name	**Ines Guttmann – Bauman, MD**
Address	**Street 707 SW Gaines St**
	City Portland
	State Oregon
	Zip Code 97239
	503-494-1933
E-mail	**guttmann@ohsu.edu**

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?

Yes
- Topic of assessment is important to address?
  Yes
- Public policy and clinical relevance are well defined?
  In general, it is well defined. However, I would think it is important to emphasize the difference between insulin requiring and non-requiring diabetes. Utilizing insulin might contribute to wider fluctuations of blood glucose and in such cases there might be a bigger benefit of using the CGM. This is particularly important for the group under 18 years old, which largely comprises of insulin-dependent patients.

Page 5 Line starting from 1 – Outcomes assessed

I am challenged by the definition of primary outcomes, as microvascular and macrovascular complications take many years to develop, and cannot be assessed adequately by a study 6 -12 months long. Fetal outcomes and c-section rates are a bit more appropriate primary outcomes, as they can be reasonably linked to intervention. However, those are the more accepted markers of overall diabetes control, and I can see why they are listed as primary outcomes, despite the fact they could not be addressed in any analysis to date.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?
  This section is very comprehensive and summarizes not only the rationale for CGM use but gives a good review of current professional societies recommendations and insurer coverage. I find it to be useful in illuminating the differences between the entities quite well. I have no specific objections to the Background session.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
  Agree.
- Key questions clearly defined and adequate for achieving aims?
  Agree.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
  Yes
- Criteria for the inclusion and exclusion of studies is appropriate?
  Yes
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
  Yes
- Data abstraction and analysis/review are adequate?
  Yes

Page 59 Line 14 onwards

Articles selected for full text review refer to chronic migraine, chronic tension-type headache and chronic daily headache. This might be a copy-paste type error.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
  Yes
- Key questions are answered?
  Yes
- Figures, tables and appendices clear and easy to read?
  Yes
- Implications of the major findings clearly stated?
  Yes
- Have gaps in the literature been dealt with adequately?
  Yes
- Recommendations address limitations of literature?
  Yes, very clearly

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?
  Yes

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

The answer to all of the above is certainly yes. The authors performed a thorough literature search, reviewed and graded the evidence appropriately. Unfortunately, the quality of evidence is predominantly low to moderate, which illustrates current limitations of research in this field. One of the important clinical points is that benefits with CGM usage increase with increased frequency of wearing the device, and the authors of this review did highlight it when the results of individual studies suggested the effect. Clearly, there is a need for studies that will address this variable more consistently and hopefully in more detail.

It is unfortunate that this review occurred prior to publication of the ”Diabetes Care” December 2017 issue, as they thematically dedicated a part of it to the review of CGM systems. It contains several relevant new consensus papers. However, my review of references used for position papers reveals no relevant studies that might have made a difference in conclusions of this review.

Lastly, in the same issue of “Diabetes Care”, there is a call for taking outcomes other than A1c into account when evaluating both clinical care and research. One of the measures that was introduced as needing more emphasis is “time in range”, which can be assessed with the help of CGM technology. I hope this will provide the community of endocrinologists with more relevant data and further illuminate the role CGM plays in achieving optimal diabetes outcomes.

QUALITY OF REPORT

(Click in the gray box to make your selection)
Superior x
Good
Fair
Poor

From: Broyles, Frances
To: HCA ST Health Tech Assessment Prog
Subject: Dexcom
Date: Monday, November 20, 2017 7:52:30 AM
Importance: High

We desperately are in need of coverage for the Dexcom CGM for Type 1 Diabetics with hypoglycemic unawareness on Medicaid. this is lifesaving and saves hundreds of thousands of dollars by avoiding ER visits, hospitalizations, 911 calls missed work and office visits. Please consider this VERY important device approval.

Fran Broyles, M.D.

Swedish System Medical Director

Diabetes, Endocrinology and Nutrition
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December 4, 2017

Health Technology Clinical Committee (HTCC)
Cherry Street Plaza
626 8th Avenue SE
Olympia, WA 98501

RE: Washington State Re-Review of CGM

On behalf of the American Association of Clinical Endocrinologists (AACE), we would like to applaud the Health Technology Clinical Committee (HTCC) consideration of coverage for continuous glucose monitoring (CGM) in the Washington state Medicaid program.

AACE represents more than 7,000 endocrinologists in the United States and abroad, including over 400 clinical endocrinologists in the State of Washington. AACE is the largest association of clinical endocrinologists in the world. The majority of AACE members are certified in Diabetes, Endocrinology and Metabolism and concentrate on the treatment of patients with endocrine and metabolic disorders including diabetes, thyroid disorders, osteoporosis, growth hormone deficiency, cholesterol disorders, hypertension and obesity.

As you deliberate coverage criteria for this important technology, AACE hopes you will consider the attached AACE and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement, which makes recommendations regarding the appropriate patient population to utilize CGM. Utilization of CGM among patients with diabetes, both type 1 and type 2, undergoing a regime of intensive insulin therapy has shown demonstrated efficacy in reducing hemoglobin A1C, the measure of blood sugar control. Improvement in blood sugar control will result in decreased complications of this dreaded disease. CGM reduces severe hypoglycemic episodes. Reduction in severe hypoglycemia episodes can decrease ER visits, accidents on highways, and even death. A broad CGM coverage decision by Washington state's Medicaid will enable physicians to prescribe CGM for their appropriate patients, thus increasing population health and reducing costs in the Medicaid system.

Once again, thank you for your decision to review coverage for CGM to the Washington state Medicaid population, AACE looks forward to your final decision.

[redacted]

Jonathan D. Leffert, MD, FACP, FACE, ECNU
President

Attachment – 1. AACE/ACE 2016 Outpatient Glucose Monitoring Consensus Statement
2. Continuous Glucose Monitoring: A Consensus Conference of the American Association of Clinical Endocrinologists and American College of Endocrinology.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY 2016 OUTPATIENT GLUCOSE MONITORING CONSENSUS STATEMENT

Timothy S. Bailey, MD, FACP, FACE, ECNU, Cochair[1];
George Grunberger, MD, FACP, FACE, Cochair[2];
Bruce W. Bode, MD, FACE[3]; Yehuda Handelsman, MD, FACP, FACE, FNLA[4];
Irl B. Hirsch, MD[5]; Lois Jovanovič, MD, MACE[6];
Victor Lawrence Roberts, MD, MBA, FACP, FACE[7];
David Rodbard, MD[8]; William V. Tamborlane, MD[9]; John Walsh, PA, CDTC[10]

This document represents the official position of the American Association of Clinical Endocrinologists and American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

From the [1]Director, AMCR Institute Escondido, California Clinical Associate Professor, University of California, San Diego School of Medicine; [2]Chairman, Grunberger Diabetes Institute; Clinical Professor, Internal Medicine and Molecular Medicine & Genetics, Wayne State University School of Medicine; Professor, Internal Medicine Oakland University William Beaumont School of Medicine Bloomfield Hills, Michigan; [3]Atlanta Diabetes Associates; Associate Professor of Medicine, Emory University School of Medicine Atlanta, Georgia; [4]Medical Director and Principal Investigator, Metabolic Institute of America; President, American College of Endocrinology Tarzana, California; [5]Professor of Medicine, University of Washington School of Medicine Seattle, Washington; [6]Physician Consultant, Sansum Diabetes Research Institute; Clinical Professor of Medicine, University of Southern California-Keck School of Medicine; Attending Physician-Santa Barbara County Health Care Services; Adjunct Professor, Biomolecular Science and Engineering and Chemical Engineering, University of California-Santa Barbara Santa Barbara, California; [7]Professor of Internal Medicine, University of Central Florida College of Medicine Orlando, Florida; [8]Chief Scientific Officer, Biomedical Informatics Consultants LLC Potomac, Maryland; [9]Professor and Chief of Pediatric Endocrinology, Yale School of Medicine New Haven, Connecticut; [10]Diabetes Clinical Specialist, AMCR Institute Escondido, California
Address correspondence to American Association of Clinical Endocrinologists, 245 Riverside Avenue, Suite 200, Jacksonville, FL 32202. E-mail: publications@aace.com. DOI: 10.4158/EP151124.CS

(Appendixes are available online at http://aace.journals.aace.com)

Abbreviations:
A1C = glycated hemoglobin; **AGP** = ambulatory glucose profile; **ARD** = absolute relative difference; **BGM** = blood glucose monitoring; **CGM** = continuous glucose monitoring; **CMS** = Centers for Medicare and Medicaid Services; **CSII** = continuous subcutaneous insulin infusion; **CV** = coefficient of variation; **DCCT** = Diabetes Control and Complications Trial; **DirecNet** = Diabetes Research in Children Network; **FDA** = US Food & Drug Administration; **GDM** = gestational diabetes mellitus; **GM** = glucose monitoring; **IDF** = International Diabetes Federation; **ISO** = International Organization for Standardization; **MARD** = mean absolute relative difference; **MDI** = multiple daily injections; **MedARD** = median absolute relative difference; **MNT** = medical nutrition therapy; **SAP** = sensor-augmented pump; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus.

INTRODUCTION

The measurement of glycemic status is a key element in the care of all persons with diabetes (1,2). Glucose monitoring (GM) enables clinicians to evaluate the efficacy of current therapy, make insulin and medication dose adjustments, ensure patients' glucose levels are within therapeutic goal ranges, and monitor treatment safety. Both capillary blood glucose monitoring (BGM) and continuous glucose monitoring (CGM) with interstitial fluid sensors enable patients to better understand the impact of diet, exercise, illness, stress, and medications on glucose levels and to recognize and treat hypoglycemic and hyperglycemic episodes. Likewise, both BGM and CGM have been shown to improve the efficacy and safety of diabetes therapy (3-12).

This document provides recommendations to clinicians regarding the type and frequency of GM technology that should be employed in the management of patients with type 1 diabetes mellitus (T1DM: pediatric or adult), type 2 diabetes mellitus (T2DM), and pregnancy complicated by pre-existing diabetes or gestational diabetes mellitus (GDM). In this document, we refer to GM technology that improves the lives of people with diabetes as "meaningful monitoring." "The scope" of this document does not extend to the complexities of insulin adjustments based on the GM data obtained. Other pivotal reference documents can be consulted for this information (13,14). **(Endocr Pract. 2016;22:231-261)**

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Additional aims of the document are to:

1. Provide a primer on GM accuracy
   a. Describe various ways to characterize accuracy, such as mean absolute relative difference (MARD)
   b. Review GM accuracy guidelines from the International Organization for Standardization (ISO) and the US Food and Drug Administration (FDA)
   c. Discuss how device accuracy has the potential to affect glucose control
2. Review measures of glycemic control (glucometrics) such as the glycated hemoglobin (A1C) laboratory measurement, change in average glucose with time, percentage of time in target, hypoglycemic and hyperglycemic ranges, and glucose frequency distribution. Graphical methods to display glycemic data will also be presented.

History of GM in Diabetes

For several decades, urine glucose testing was the mainstay of diabetes monitoring (15). While patients could perform measurements at home and potentially adjust their therapy, the shortcomings of urine glucose testing were well recognized. Urine glucose correlated very poorly with blood glucose levels, provided no information about hypoglycemia, and gave negative results until the renal threshold for glucose excretion was exceeded. Therefore, urine glucose testing is presently of historical interest only.

The colorimetric Dextrostix® glucose test strip was developed in 1965. It was used for the first blood glucose meter in 1970 (15). Starting in the late 1970s, daily BGM gained wider acceptance as research data began to support the correlation and causation between poor glycemic control and diabetic complications (15-23). The "glucose hypothesis" was confirmed in the landmark Diabetes Control and Complications Trial (DCCT), the first long-term randomized prospective study to compare intensive (≥4x/day) self-GM coupled with an insulin titration algorithm versus standard therapy using once-daily GM and 1 to 2 daily insulin injections (24). Intensive therapy delayed the onset and slowed the progression of microvascular complications in patients with T1DM. Following the publication of the DCCT results in 1993, the value of BGM in T1DM management became widely accepted, and its use gradually increased. It was clear that intensive insulin therapy and self-adjustment of insulin dosage in T1DM required frequent BGM (9,13,25-27). Subsequently, the effectiveness of BGM in GDM was demonstrated.

The value of BGM in T2DM has been controversial. As shown in Table 1, studies of BGM in T2DM have presented mixed conclusions. Several have shown a clear benefit from frequent BGM (11,12,28-30). This has been particularly evident for patients with T2DM who are receiving insulin therapy, especially involving multiple daily injections (MDI), "basal-bolus" therapy, or insulin pump (continuous subcutaneous insulin infusion) (31). Newer studies using a more structured testing approach have suggested benefit even for persons with diabetes not receiving insulin (9); these data support the need for patient education to ensure that each measured glucose leads to an action plan.

There is a common misperception that BGM is an expensive, complex undertaking with limited benefit, leading some to assert that BGM is not warranted in patients with T2DM (32-35). The studies that appear to give negative results in patients with T2DM have been criticized for serious experimental design flaws (28). Several studies included rapid intensification of medication regimens following diagnosis, which may have obscured the effect of BGM. Additionally, many studies failed to couple GM to therapy adjustment, thus attenuating the benefit of the monitoring (28).

While BGM is a widely used and important component of T1DM therapy, it has drawbacks: patients' monitoring may be infrequent or intermittent, their reports may be inaccurate, and overnight glucose levels are seldom measured. Given these limitations, episodes of hypo- and hyperglycemia may be missed and not factored into treatment decisions (26,36). CGM offers the potential to revolutionize patient treatment by providing more frequent information that may allow a greater proportion

Table 1
Key Studies of BGM in T2DM (7,9-12,29,30,32-34,183-185)

T2DM: Evaluation of the role of BGM	
Pro: Use of BGM significantly improves glycemic control and/or reduces risk of hypoglycemia	**Con: Use of BGM does *not* significantly improve glycemic control and/or reduce risk of hypoglycemia**
Observational studies	
ROSSO (12) Karter, et al (Kaiser Permanente) (29)	Freemantle Diabetes Study (183) QuED (184)
Randomized controlled trials	
German-Austrian (30) DINAMIC (111) ASIA (185) SteP (9) ROSES (7) St. Carlos (10)	King-Drew Medical Center (34) ESMON (32) DiGEM (33)

Abbreviations: ASIA = Auto-Surveillance Intervention Active Study; BGM = blood glucose monitoring; DiGEM = Diabetes Glycaemic Education and Monitoring Study; DINAMIC 1 = Diamicron MR in NIDDM: Assessing Management and Improving Control; ESMON = Efficacy of Self Monitoring of Blood Glucose in Patients with Newly Diagnosed Type 2 Diabetes Study; QuED = Quality of Care and Outcomes in Type 2 Diabetes Study; ROSES = Role of Self-Monitoring of Blood Glucose and Intensive Education in Patients with Type 2 Diabetes Not Receiving Insulin Study; ROSSO = Retrolective Study "Self-monitoring of Blood Glucose and Outcome in Patients with Type 2 Diabetes"; SteP = Structured Testing Protocol Study; T2DM = type 2 diabetes mellitus.

of patients to achieve target glucose and A1C levels with greater safety.

The first CGM device was approved in the United States in 1999. The MiniMed CGM System sampled glucose through a subcutaneously implanted sensor, recording glucose levels every 5 minutes over a period of 3 days. Initial versions of this technology did not provide glucose values in real time; data were downloaded and retrospectively evaluated by clinicians and used to make treatment adjustments (26). The first real-time CGM for prospective patient use was approved in 2001 (Glucowatch Biographer; Cygnus Inc, San Francisco, CA). The device used reverse iontophoresis to sample blood glucose, providing approximately 36 measurements directly to patients over the 12-hour life of the sensor (37). It was withdrawn from the market due to skin site reactions, discomfort, limited accuracy, and difficult setup and calibration procedures (38). Since then, CGM technology has improved dramatically in terms of accuracy, usability, and duration of use. The landmark Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group trial (6) established the role of CGM in T1DM, demonstrating significant A1C reductions in adults. The magnitude of benefit correlated positively with both wearing and interacting with the technology (4). In patients with lower baseline A1C, there were smaller reductions in A1C, but a reduction in hypoglycemia (39). These benefits persisted for up to 12 months (40). Other unmasked parallel-group studies have confirmed significant reductions in A1C and a trend for reductions in severe hypoglycemia (3,4,41,42). A summary of trial results for A1C and hypoglycemia reduction with CGM is shown in Figure 1.

CGM has the ability to provide alerts to actual or predicted episodes of hypo- and hyperglycemia. Further, all modern-day sensor devices display arrows reflecting the current slope of glucose versus time, which can assist clinical decision-making by the patient. However, CGM technology has drawbacks including expense; a need to frequently calibrate most devices; and some issues related to accuracy, comfort, convenience, and patient acceptance.

Current Status of GM

Previous publications from the American Association of Clinical Endocrinologists (AACE), Endocrine Society, and American Diabetes Association (ADA), provide sound general recommendations to guide diabetes therapy based on personal glucose records and laboratory values (1,2,28,43,44). No clinician caring for patients with diabetes would dispute the value of employing some form of GM.

The Effective Health Care Program of the US Agency for Healthcare Research and Quality conducted comparative effectiveness research assessing GM methods and intensive insulin therapy methods. This included effectiveness studies comparing real-time CGM to BGM in adults, adolescents, and children with T1DM (45). While methods of GM did not affect patient quality of life, A1C was lowered by 0.3% in patients who used CGM compared with

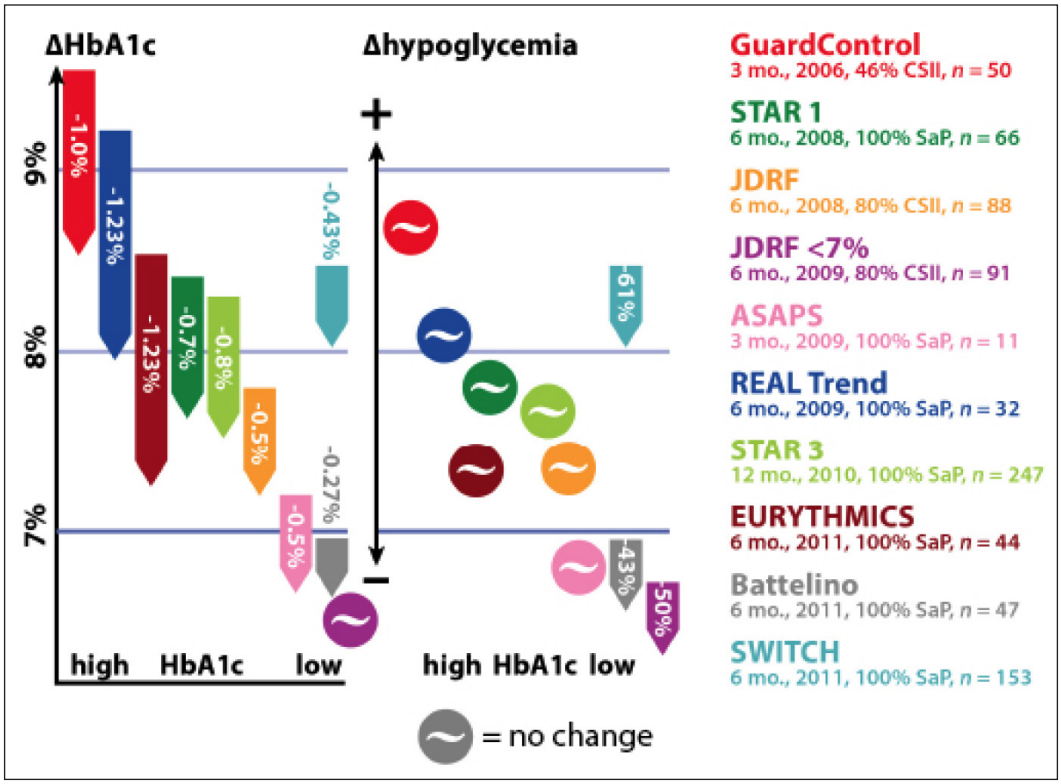


Fig. 1. Glycated hemoglobin and hypoglycemia reductions in continuous glucose monitoring studies (189).

patients who used BGM. This positive outcome for CGM was consistent for patients <18 years of age, supporting its use in adolescent patients and children. Unfortunately, because GM is a substantial cost driver in the management of patients with diabetes (28,46,47), governments and insurance companies have restricted coverage, payments, and reimbursement. However, improvements in A1C and accompanying reductions in hypoglycemia have been used to justify the cost of newer diabetes medications. To the extent that GM can also enable patients to achieve lower A1C values with less hypoglycemia, a similar and stronger case can be made for increasing access to GM (48), particularly as costs come down and evidence continues to show benefit for both T1DM and T2DM. For patients who use insulin, CGM offers the distinct advantage of being able to securely maintain a more normal glucose range with less risk of hypoglycemia. As of the writing of this document, there remains no CGM coverage for elderly patients with T1DM, a population with frequent and severe hypoglycemia (49).

Over the last 30 years, the FDA has approved many monitor models for use in GM. Since 2003, the FDA has required the accuracy of BGM devices to be within 20% of the true value at least 95% of the time (50). Certain monitors have shown substantially greater variability than allowed by FDA standards, leading to the recall of several brands of glucose meters and test strips in 2013 (51-54). The importance of GM accuracy and the emergence of stricter accuracy standards are discussed in greater detail in the "GM Accuracy and Precision" section later in this manuscript.

In 2013, the US Centers for Medicare and Medicaid Services (CMS) implemented the controversial process of competitive bidding for BGM meters and test strips, with the intended goal of cost savings (55). This was one factor that led to a surge in the number and types of "generic" BGM meters. In some cases, when meters sourced from retail distribution channels were tested, the generic testing systems meters demonstrated dramatically inferior accuracy and precision compared to systems from major branded manufacturers (56-59). These generic meters showed sufficient performance data to obtain initial FDA clearance; however, they may not have maintained adequate performance over time, in part due to poor quality control leading to large between-lot variability in test strips. One proposed response has been to require postmarket surveillance of BGM products (60-62). The CMS competitive bidding process may have had other unintended consequences. A recent analysis of CMS data by the National Minority Quality Forum (NMQF) found that test areas in which competitive bidding was initially implemented had substantial disruptions in BGM supply acquisition compared to nontest markets (23% increase in partial acquisition vs. 1.7% in nontest markets) (63). Within the test markets, decreases in full acquisition (14.4%) and increases in migration from full to partial acquisition (58.1%) were

significant ($P<.0001$ for both) (64). Patients in these markets had increased mortality and hospitalization rates and increased medical costs (63,64). Based on these results, the NMQF has called for the CMS to suspend competitive bidding until proper safety review and monitoring can be implemented (65).

The purpose of the next section of this document, "GM Strategy and Rationale by Patient Profile," is to provide concise and specific recommendations for clinicians on the type, frequency, and intensity of GM within the framework of specific patient profiles. The intent is to help clinicians counsel their patients to meaningfully monitor their glucose levels to optimize their diabetes care.

GM STRATEGY AND RATIONALE BY PATIENT PROFILE T1DM

T1DM currently constitutes 5 to 10% of all people with diabetes globally (66,67). GM is one of the essential elements of effective T1DM management (68,69). The Type 1 Diabetes Exchange Clinic Registry (2013) found a systematic, statistically significant decrease in A1C levels in relation to increased frequency of daily BGM in children, adolescents, and adults (Fig. 2) (70).

Adult Patients With T1DM

People with T1DM experience much greater glycemic variability than those with T2DM (71). This variability is associated with a higher risk of hypoglycemia (72). GM has a role in the early detection of hypoglycemia prior to overt symptoms.

BGM provides patients with important information regarding treatment efficacy (68,69). BGM can also facilitate appropriate modifications to the therapeutic regimen, providing critical information that clinicians need to adjust dosage and/or timing of basal and bolus insulins, as well as reflecting the impact of food intake and physical activity (2,68,73). Use of BGM is supported by clinical data: the DCCT, Epidemiology of Diabetes Interventions and Complications (EDIC), and many other clinical trials have clearly established the usefulness of BGM toward achieving the goals of improved glycemic control and decreasing the risk of diabetes-related complications in T1DM (2,74).

In all patients with T1DM, a rational and effective insulin regimen requires frequent GM. Frequent BGM is endorsed in all major clinical practice guidelines, including AACE, the ADA, the American Association of Diabetes Educators, the Joslin Diabetes Center, and the International Diabetes Federation (IDF) (2,28,68,73,75). Table 2 lists major organizations' general recommendations for BGM timing and glucose goals in patients with T1DM. Current guidelines advise patients to check their blood glucose frequently; recommendations range from at least 4 to 6 to 10 or more times per day. All guidelines emphasize the need for individualization for each patient, with more or less frequent monitoring before meals, postprandially, at bedtime, before exercise, and when undertaking potentially hazardous tasks (e.g., driving) (2,68,69). Patients with T1DM should also monitor their blood glucose before driving and should not drive if their glucose level is <90 mg/dL (5.0 mmol/L).

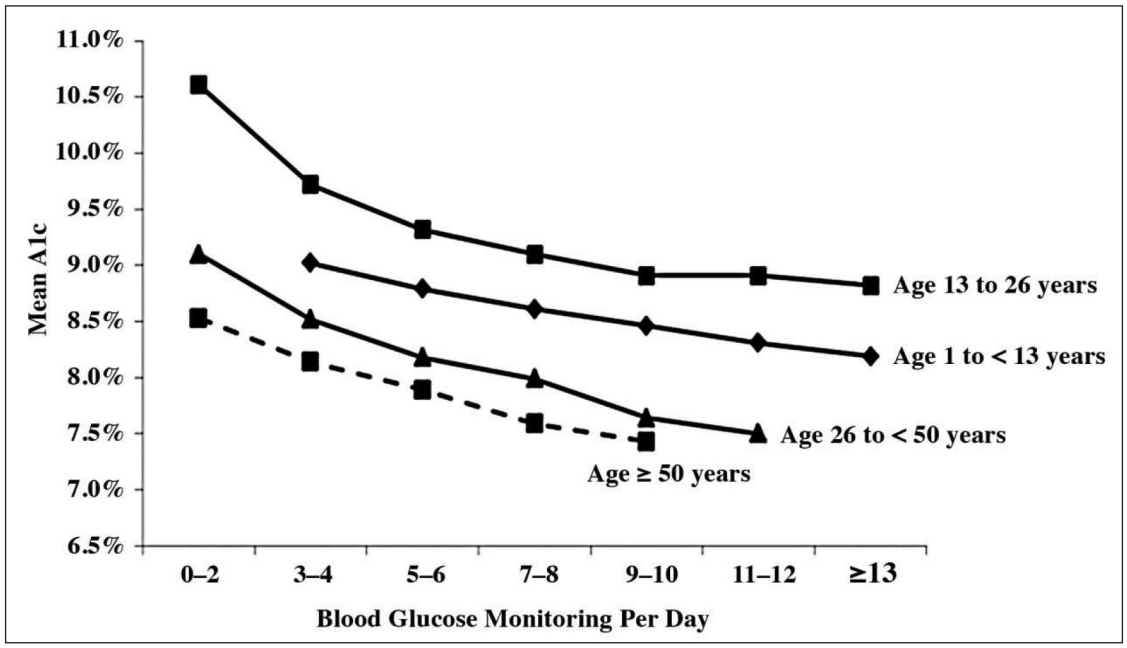


Fig. 2. Association between blood glucose monitoring frequency and A1C in patients with T1DM (70). *A1C* = glycated hemoglobin; *T1DM* = type 1 diabetes mellitus.

Table 2
Recommendations for Daily Blood Glucose Testing in Patients with Type 1 Diabetes (2,68,69)

	Timing	Goal	
		mg/dL	mmol/L
Fasting plasma glucose	Test on awakening and before meals	80-130 (ADA) 70-130 (Joslin) <110 (AACE)	4.2-7.2 (ADA) 3.9-7.2 (Joslin) <6.1 (AACE)
Postprandial	2 hours after meal 1-2 hours after meal	<180 (ADA) <180 (Joslin) <140 (AACE)	<10.0 (ADA) <10.0 (Joslin) <7.8 (AACE)
Bedtime glucose	At bedtime	90-150 (Joslin)	5.0-8.3 (Joslin)
These goals must be individualized to personal patient needs regarding pregnancy, hypoglycemia unawareness, patients who live alone, or occupational hazards that require further reduction of risk of hypoglycemia (2,68).			
Abbreviations: AACE = American Association of Clinical Endocrinologists; ADA = American Diabetes Association; Joslin = Joslin Diabetes Center.			

These guidelines also recommend the use of CGM, particularly for patients with a history of severe hypoglycemia or hypoglycemia unawareness (1,2,44,68). Once again, the timing and frequency of monitoring must be individualized to meet specific patient needs (2,28). Table A1 in Appendix A of this document summarizes pivotal trials of CGM in adult and pediatric patients with T1DM.

Pediatric Patients With T1DM

BGM remains a cornerstone for achieving optimal metabolic control in children, adolescents, and adults with T1DM (70). Frequent BGM, with a minimum of 4 blood glucose tests per day (premeal and at bedtime), should be the goal. In addition to these traditional 4 tests, many patients can gain a more robust picture of daily glucose trends by strategically adding additional tests, such as 2 hours after meals, overnight, and before and after exercise (76).

Optimal glycemic control of T1DM is particularly difficult to achieve in pediatric patients. Food intake and activity are unpredictable in very young patients, complicating parents' efforts to regulate glucose levels. Additionally, many parents experience a "Scylla and Charybdis" situation, where their fear that severe hypoglycemia will cause irreparable brain damage may lead to allowing a child's glucose to "run high." Data from the Type 1 Diabetes Exchange Clinic Registry indicate that children with elevated blood glucose and A1C levels are not protected against severe hypoglycemic events (77). Moreover, recent evidence from the Diabetes Research in Children Network (DirecNet) indicates that hyperglycemia is at least as detrimental to normal brain development as hypoglycemia (78). In adolescents, the emotional fatigue of managing their diabetes often leads to a reduced frequency of BGM, missed insulin doses, and markedly elevated A1C levels. In older children and adolescents, the adverse effects of prolonged hyperglycemia on the cardiovascular system outweigh the potential harm from hypoglycemia (79), particularly as treatment modalities and hypoglycemia management strategies have improved (2).

Another special challenge of managing T1DM during childhood and adolescence is that insulin requirements change frequently. Simply measuring blood glucose and giving immediate correction doses are insufficient for long-term glycemic control in pediatric patients. Physicians, parents, and patients need to be instructed on how to recognize trends that indicate the patient has outgrown their insulin dose(s) and learn to make longer-term regimen adjustments (80). Such pattern recognition requires maintaining and periodically reviewing an electronic or written log of blood glucose levels. Unfortunately, only a small proportion of physicians, patients, and families are downloading data from glucose meters to appropriate computer programs; reviewing glucose meter data (including multiple graphs and statistics); and carefully making thoughtful, appropriate insulin dosage self-adjustments on a systematic, periodic basis (81,82).

As in the case of BGM, CGM is only as beneficial as the patient's desire and ability to use it. It is essential that all CGM users know the basics of sensor insertion, calibration, and real-time data interpretation. To maintain a high frequency of use, patients and their parents require in-depth training with reinforcement, including periodic follow-up with clinicians and diabetes educators. The results of the JDRF CGM Study Group, using all the first-generation CGM devices available at that time (2007), showed that

children, adolescents, and young adults (aged 8-24 years) who used the sensor almost every day benefitted clinically. Unfortunately, a much lower percentage of children and adolescents (34%) than adults (59%) performed daily CGM (83).

DirecNet studied the efficacy and safety of CGM in children <10 years of age. In a randomized clinical trial of 146 patients aged 4 to 9 years, CGM did not improve metabolic control. Despite a high degree of parental satisfaction with CGM, at the end of the 6-month study, only 41% of families reported daily CGM use (42). Similar results were reported by DirecNet in a nonrandomized, 6-month pilot study of 23 children <4 years of age (84). These studies were performed with older devices; the improved accuracy and ease of use of current devices might be better accepted. However, in a recent update of the state of the art of treatment of T1DM in the US, the T1D Exchange reported that <5% of youth <18 years old were currently utilizing a CGM device (85).

Combination of continuous subcutaneous insulin infusion and CGM (sensor-augmented pump)

The Sensor-Augmented Pump Therapy for A1C Reduction (STAR 3) Study (2012) examined a system that combines the use of a continuous subcutaneous insulin infusion (CSII) pump and a CGM system, termed sensor-augmented pump (SAP) therapy. In this 1-year study, children (aged 7-12) and adolescents (ages 13-18) with T1DM and baseline A1C ranging from 7.4 to 9.5% were randomized to either SAP or MDI therapy. Overall, patients in the SAP group had significantly improved ($P<.05$) A1C values compared with the MDI group at all postbaseline visits (86). Furthermore, children and adolescents in the SAP group were consistently more likely to meet age-specific A1C targets (88% and 57%, respectively) compared with those in the MDI group (51% and 13%, respectively) (86). Children and adolescents in the SAP group had lower area under the curve values than the MDI group, without increased risk of hypoglycemia, as well as improved glucose variability (86). STAR 3 was the first study to examine the efficacy and safety of switching from conventional injections and BGM to 2 advanced technologies (CGM + CSII) nearly simultaneously; prior studies had only evaluated the impact of a single technology.

A SAP system with threshold suspend functionality was approved by the FDA in 2013 following considerable experience in Europe. This device can suspend insulin delivery for up to 2 hours when the sensor glucose value reaches a predetermined lower threshold (87). The improved accuracy of CGM sensors and this threshold suspend (called "low glucose suspend" in Europe) may increase the performance and frequency of CGM use in pediatric patients. More recent studies have indicated the effectiveness of the predictive low glucose suspend system in children (88).

An international group of leading pediatric diabetologists issued a 2012 consensus statement regarding the use of CGM in children (89). They recommended that CGM be considered for regular daily use in children and adolescents with T1DM who:

- Are performing frequent BGM
- Have experienced severe hypoglycemic episodes
- Have hypoglycemic unawareness, especially in young children
- Have nocturnal hypoglycemia
- Have wide glucose excursions, regardless of A1C
- Have suboptimal glycemic control, with A1C exceeding the target range
- Have A1C levels <7% and wish to maintain target glycemic control while limiting hypoglycemia risk

Accordingly, CGM is potentially applicable and desirable in most children with diabetes. Recent enhancements have made it possible for parents and others to monitor glucose levels continuously via smartphones, wristwatches, and computers. In 2015, the FDA approved marketing of 3 such systems: Dexcom Share (90), Dexcom G5 with Bluetooth (91), and MiniMed Connect (92). An open-source system (not FDA approved) called Nightscout was created (hacked together) by a group of people with diabetes and their families to allow remote monitoring by parents of children with diabetes (93). Other companies are likely to follow, as anecdotal reports suggest that parents and other caregivers find the technology invaluable when their children are away from home or participating in sports. Randomized controlled trial results evaluating these technologies are not available.

T2DM

Adult Patients with T2DM

BGM is an essential tool that should be accessible to all patients with T2DM, regardless of whether or not they are receiving insulin treatment (28). BGM is clearly beneficial for adult patients with T2DM because it provides immediate feedback regarding glycemic control (rather than requiring waiting, possibly months, for the next A1C measurement), and it assists with patient education, understanding, and behaviors. Table A2 in Appendix A of this document summarizes pivotal trials of GM in adult patients with T2DM.

To ensure meaningful monitoring, use of BGM in patients with T2DM must be individualized by the physician and healthcare team in partnership with the patient. The patient should be given specific guidelines including frequency and timing of testing and taught how to communicate these results to the healthcare team. Methods for communication of glucose data are shown in Table 3. Two

of the goals for any BGM strategy are to empower patients to play a more active role in their diabetes management and to maximize the efficacy and safety of glucose-lowering therapies, including lifestyle management (94). GM results are also a vital component of the data that should be presented to the diabetes care clinician at each medical appointment, and potentially between visits, to assist in therapy titration.

Several randomized trials and literature reviews have called into question the clinical utility and cost-effectiveness of routine BGM in patients with T2DM who are not receiving insulin therapy (32,33,35,95,96). A key consideration is that BGM, used alone, does not lower blood glucose levels. To be useful, the information must be *communicated* to the healthcare team in an effective and timely manner and integrated into self-management plans. Several recent trials of structured BGM included specific instructions on testing frequency and timing, interpreting and communicating these results, and integrating results into self-management plans. These studies have shown improved glycemic control in patients with T2DM who do not receive insulin therapy (8,9,97,98).

General guidelines on the frequency and timing of testing based on specific patients' diabetes therapy are presented below and are outlined in Table 4.

GM in patients with T2DM on insulin therapy

If the patient is on intensive insulin therapy using prandial insulin combined with basal insulin, BGM should be performed when fasting, premeal, at bedtime, and periodically in the middle of the night. Such monitoring allows for appropriate adjustment of doses of premeal insulin, correction boluses, and basal insulin.

If the patient is receiving only basal insulin, with or without other diabetes medications, BGM should be performed at minimum when fasting and also at bedtime to evaluate the impact of basal insulin on lowering overnight glycemic levels. If the decline in Bedtime to AM (morning) glucose (known as the BeAM factor) is >55 mg/dL (3.1 mmol/L), this suggests an excessive basal insulin dose (99), just as an overnight rise in glucose levels may indicate a need to increase basal insulin. Before titrating basal insulin to higher doses, consider improving the bedtime glucose by other means (e.g., with prandial insulin administered before dinner). This may prevent nocturnal hypoglycemia caused by excessive basal insulin and lead to improved overall glycemic control (31). If the patient is receiving basal insulin combined with 1 daily prandial or premixed insulin injection, BGM should be performed at minimum when fasting and before the prandial or premixed insulin and periodically at other times (i.e., premeal, bedtime, 3 AM, and possibly 2 hours postprandially). Insulin adjustments should be made to achieve acceptable glycemic targets.

GM in patients with T2DM on noninsulin therapies

The IDF published a 2009 guideline specific to BGM in noninsulin-treated patients with T2DM (28). The IDF recommends that:

1. BGM should only be used when patients and/or caregivers have the knowledge, skills, and willingness to incorporate both BGM monitoring and accompanying therapeutic adjustments into their diabetes care plan.
2. BGM is only appropriate if protocols are individualized to meet their patients' educational/behavioral/clinical requirements and have been mutually agreed upon by the patient and clinician.
3. BGM should be considered both at the time of diagnosis, to enhance patient education and facilitate treatment initiation, and as part of ongoing diabetes self-management education. The goal is to help patients actively and effectively participate in their treatment.

GM in patients with T2DM on noninsulin therapies associated with frequent or severe clinical problems related to hypoglycemia

Patients with T2DM receiving noninsulin agents associated with elevated hypoglycemia risk (specifically, sulfonylureas, and glinides) should perform BGM at least once daily (fasting) and periodically at other times to confirm the effectiveness of therapy and detect possible hypoglycemia. Appropriate therapeutic adjustments should be made

Table 3
Methods for Communication of Glucose Data

1. Logbook at time of office visit
2. Computer outputs (graphs, statistics, interpretation) generated by patient or clinic staff, immediately before or at time of office visit
3. Periodic phone calls, faxes, or emails to office
4. Automated transfer from meter or sensor to Internet for review
5. Automated interpretation by the glucose monitoring device displayed on its screen (e.g., "Your before-lunch glucose has been running high")

Table 4
Use of Glucose Monitoring Technology by Diabetes Type (1,2,44,48,68,76,80,101,107,115-120,186)

Diabetes type	BGM recommendations	CGM recommendations
Type 1 – Adult	At least twice per day to 6-10 times per day, including before meals, occasionally postprandially, before exercise or critical tasks (e.g., driving), and at bedtime.	CGM recommended, particularly for patients with history of severe hypoglycemia, hypoglycemia unawareness and to assist in the correction of hyperglycemia in patients not at goal. CGM users must know basics of sensor insertion, calibration, and real-time data interpretation.
Type 1 – Pediatric	At least 4 times per day, including before eating and at bedtime. A more accurate picture of daily glucose trends may be gained with additional testing, including 1-2 hours after meals, overnight, and before/after exercise. Insulin requirements for pediatric patients change frequently. Physicians, patients, and caregivers should learn to recognize glucose trends that indicate that the insulin regimen requires adjustment. This requires maintaining and periodically reviewing electronic or written logs of BG levels.	Same as Adult Type 1. Both prevalence and persistent use of CGM is lower in children than adults. More in-depth training as well as more frequent follow-up is recommended to enable children to adopt the technology more successfully.
Type 2 – Receiving insulin/ sulfonylureas, glinides	Structured BGM is recommended. BGM in patients on intensive insulin: fasting, premeal, bedtime, and periodically in the middle of the night. BGM in patients on insulin ± other diabetes medication: at minimum, when fasting and at bedtime. BGM in patients on basal insulin + 1 daily prandial or premixed insulin injection: at minimum when fasting and before the prandial or premixed insulin, and periodically at other times (i.e., premeal, bedtime, 3 AM). Additional testing before exercise or critical tasks (e.g., driving) as needed.	Data on CGM in T2DM are limited at this time. Trials assessing the use of CGM in T2DM patients are ongoing.
Type 2 – Low risk of hypoglycemia	Daily BGM not recommended. Initial periodic structured BGM (e.g., at meals and bedtime) may be useful in helping patients understand effectiveness of MNT/ lifestyle therapy. Once at A1C goal, less frequent monitoring is acceptable.	No recommendation.
Gestational	Patients not receiving insulin: fasting and 1 hour postprandial. Patients receiving insulin: fasting, preprandial, and 1 hour postprandial.	Benefits of CGM in pregnant females with pre-existing diabetes are unclear based on current data; additional studies are ongoing. CGM during pregnancy can be used as a teaching tool, to evaluate glucose patterns, and to fine-tune insulin dosing. CGM in pregnancy can supplement BGM, in particular for monitoring nocturnal hypoglycemia or hyperglycemia and postprandial hyperglycemia.

Abbreviations: A1C = glycated hemoglobin; BG = blood glucose; BGM = blood glucose monitoring; CGM = continuous glucose monitoring; MNT = medical nutrition therapy; T2DM = type 2 diabetes mellitus.

if patients are not at goal. Consideration should be given to altering therapy to employ 1 or more of the multiple classes that are not associated (or minimally associated) with increased risk of hypoglycemia (e.g., metformin, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose cotransporter-2 [SGLT-2] inhibitors, thiazolidinediones [TZDs], or glucagon-like peptide-1 [GLP-1] receptor agonists).

GM in patients with T2DM on noninsulin therapies not associated with hypoglycemia

Patients with T2DM receiving treatment regimens not typically associated with increased risk of hypoglycemia and who are not at goal should be instructed to perform structured testing (e.g., systematically before meals and at bedtime) at least weekly to adjust and confirm therapeutic effectiveness (9). Patients should be educated about when and how frequently to monitor glucose and should record the data in an organized logbook for subsequent review by a diabetes professional. Guidance for communication of glucose data is outlined in Table 3. After the A1C goal has been reached, and in the absence of evidence of hypoglycemia, then less frequent monitoring may be necessary.

GM in patients with T2DM on diet/lifestyle therapy only

Daily BGM has not been shown to be effective in patients on diet/lifestyle therapy who are at low risk for hypoglycemia (28,33,35,94). However, structured testing may help patients improve their understanding of the effectiveness of medical nutrition therapy (MNT) and lifestyle management. Initial periodic testing at meals and bedtime provides feedback to the patient regarding the impact of various foods and physical activity on glycemic levels. After the goal A1C has been achieved, less frequent monitoring may be needed.

Use of CGM in patients with T2DM

There are limited data on the use of real-time CGM in patients with T2DM, either masked for retrospective analysis or unmasked for real-time use. Several studies have evaluated masked CGM, in which patients cannot see glucose values in real time, to help understand the progression from nondiabetes to prediabetes and T2DM (100). Other trials are ongoing to evaluate the potential use of masked CGM to guide both patients and clinicians regarding appropriate medication and lifestyle changes to improve glycemic control. Real-time CGM trials in T2DM patients are also ongoing, with several randomized controlled trials completed in recent years.

Vigersky et al compared real-time CGM (used for 8 of the initial 12 weeks of the study) to BGM 4 times a day in 100 patients with T2DM who were being treated with diet and exercise alone or with glucose-lowering therapies other than prandial insulin. At 12, 24, 38, and 52 weeks, respectively, this study found mean, unadjusted A1C decreases of 1.0%, 1.2%, 0.8%, and 0.8% in the CGM group compared with 0.5%, 0.5%, 0.5%, and 0.2% in the BGM group (P = .04). The reduction in A1C over the study period remained significantly greater in the CGM versus BGM group after adjusting for covariates (P<.0001). Patients who used CGM for at least 48 days showed the most improvement (P<.0001) (48).

A multicenter trial randomized 57 insulin-treated patients with T2DM to real-time CGM versus Internet-based BGM monitoring; results showed a greater reduction in A1C in the CGM group (1.31%) compared to the BGM group (0.83%), although the difference was not statistically significant (101). Additional randomized trials of CGM will be helpful in the evaluation of the benefits of CGM in T2DM.

Pregnancy Complicated by Diabetes

Approximately 8% of US pregnancies are complicated by either GDM or pre-existing T1DM or T2DM (102-104). In the early weeks of pregnancy, the excessively high maternal glucose levels of patients with poorly controlled or undiagnosed T1DM and T2DM are associated with an increased risk of miscarriage and congenital malformations (103,105). Hyperglycemia during the second and third trimesters results in fetal hyperinsulinemia that increases the risk of macrosomia and neonatal hypoglycemia (106,107). Maintenance of maternal glycemia as close to normal as possible through a program of BGM (or CGM), MNT, and insulin therapy offers the most effective protection against these complications (108).

The feasibility and efficacy of BGM in pregnancy complicated by diabetes were demonstrated in a seminal 1980 clinical trial that used BGM (8 measurements per day), MNT, and basal (neutral protamine Hagedorn) plus regular insulin in pregnant patients with T1DM (n = 10). All patients achieved normal mean plasma glucose and A1C levels, and the infants showed no signs of diabetes-related complications (109). Today, BGM is integral to the management of diabetes in pregnancy (104). Real-time results enable individuals to make informed daily self-care decisions regarding diet, exercise, and insulin. Retrospective analysis of BGM data enables clinicians to develop individualized care plans (110), informing decisions related to insulin initiation and adjustment and the possible needs for interventions or hospitalization to improve inadequate self-monitoring (111).

CGM generates a detailed profile of glucose excursions that can be helpful when making decisions regarding self-care and treatment planning. Currently available CGM devices do not measure blood glucose levels <70 mg/dL (3.9 mmol/L) very accurately (112-114). Nevertheless, CGM can identify many episodes of hypo- and hyperglycemia that would go undetected by BGM (108,115). CGM appears superior to BGM in this regard, but it remains to be seen whether CGM improves pregnancy outcomes. A 2013

trial comparing BGM alone to BGM combined with several 6-day periods of unmasked CGM in pregnant women with T1DM or T2DM (n = 154) found no differences in maternal A1C at term or in neonatal morbidity. Only 64% of the patients in that study were fully compliant with the CGM protocol, so potential benefits may have been missed. The most common reasons for noncompliance were device discomfort, sleep disturbances caused by alarms, and sensor inaccuracy (116).

The potential benefit of CGM for pregnant women with pre-existing diabetes is unclear based on currently available data. A prospective, randomized controlled trial performed in the United Kingdom assigned 71 pregnant females with T1DM or T2DM to prenatal care with or without CGM (117). While no maternal A1C differences were observed at baseline or throughout the first 2 trimesters, patients in the CGM group began to experience lower A1C levels between weeks 28 and 32, a difference that became statistically significant by weeks 32 to 36 (5.8% vs. 6.4%, P = .007). In contrast, a Danish trial that randomized 123 pregnant females with T1DM or T2DM to routine prenatal care alone or similar care plus CGM did not find any differences in outcomes between the 2 groups (118). Another randomized controlled trial of 340 Chinese females with GDM found that the use of CGM combined with standard care led to decreased A1C levels and less severe glycemic excursions compared to standard care alone (P<.001). Additionally, the use of CGM decreased the risk of pre-eclampsia and cesarean birth (P = .019 and P = .028, respectively) (119).

An ongoing study, the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT, expected completion in late 2015), will attempt to determine if real-time CGM can safely improve glycemic control in patients with T1DM who are pregnant or planning pregnancy; this study will also assess infant outcomes (120).

CGM during pregnancy should be regarded as a teaching tool to evaluate peak postprandial blood glucose, fine-tune insulin dosing, and identify foods associated with blood glucose spikes (116). CGM can also be used as an adjunct to BGM to monitor nocturnal hypoglycemia and hyperglycemia, as well as the peak and duration of postprandial hyperglycemia. A 2007 clinical trial of CGM in pregnancy reported that the additional information provided by CGM altered clinical management decisions in 62% of cases (this trial did not evaluate patient outcomes) (121).

Table A3 in Appendix A of this document summarizes pivotal trials of BGM and CGM in patients with pregnancy complicated by diabetes. Blood glucose goals and recommended BGM patterns during and prior to pregnancy are summarized in Table 5.

Before attempting to become pregnant, females with pre-existing diabetes should maintain glycemic control as close to normal as possible for 3 to 6 months. Preprandial and fasting blood glucose should be maintained in the 60 to 90 mg/dL range, and postprandial glucose tested at 1-hour postmeal should be between 100 and 120 mg/dL (107).

The typical target fasting plasma glucose range during pregnancy complicated by diabetes is 55 to 90 mg/dL (3.1 to 5.0 mmol/L). This implies a heightened risk of hypoglycemia. Accordingly, meter accuracy in the low blood glucose ranges is critically important in patients with pregnancy complicated by diabetes. Hypoglycemia, in particular asymptomatic hypoglycemia, is a key safety concern during pregnancy. Pregnant females with diabetes should monitor their blood glucose before driving and should not drive if their glucose level is <90 mg/dL (5.0 mmol/L). Likewise, they should always keep appropriate carbohydrate snacks with them in the car in case they become hypoglycemic.

GM ACCURACY, PRECISION, AND DATA DISPLAY METRICS

Accuracy (the ability to obtain a true value without systemic bias) and precision (the ability to obtain highly reproducible results) have been steadily improving since the introduction of BGM in the 1970s. A 1986 ADA consensus conference, convened at a time when an estimated 1 million people with diabetes were using BGM, concluded that more than 50% of glucose meter measurements deviated by more than 20% from a reference method. This was

Table 5
Recommendations for Daily Blood Glucose Testing in Pregnancy Complicated by Diabetes (103)

	Timing	Goal	
		mg/dL	mmol/L
Fasting	On awakening	60-90	3.3-5.0
Preprandial	Before every meal	60-90	3.3-5.0
1-hour postprandial	1 hour after every meal	100-120	5.6-6.7

attributed to both system and human factors. The ADA stated an aspirational goal in 1987 that 100% of BGM readings be within 10% of reference values (122). In 1993, a similar panel was convened and recommended that the analytic error not exceed 5% (123). Since it is only recently that any devices have even approached such performance, regulatory criteria for device approval have been more pragmatic, focusing on the hazards of incorrect readings (e.g., suboptimal treatment decisions, including improper adjustments in medication dosage, potentially increasing the frequency of both hypoglycemia and hyperglycemia) (58).

Accuracy, ergonomics, and ease of use of blood glucose meters have improved dramatically over time (124-126), and the accuracy of CGM is beginning to approach that of BGM devices (113,114,127-130). However, a clinically significant variation in accuracy and precision persists among currently marketed GM devices. Clinicians must be familiar with the clinical and laboratory standards used to characterize the accuracy and precision of the devices that they recommend in order to work safely and most effectively with patients using BGM or CGM systems.

Measures of BGM and CGM Accuracy

There is a logical progression as to how one should interpret performance data with the objective of choosing the appropriate GM device for a particular patient. The following presents such an approach.

(*1*) Bias. This refers to any systematic error in the measurements provided by the meter or sensor. This may be due to improper calibration, lack of calibration, or calibration with an inaccurate BGM. Bias may vary depending on the glucose levels being measured.

(*2*) Precision: Precision refers to the reproducibility of measurements, irrespective of whether they accurately measure the true value they are supposed to be measuring. Measurements may be highly reproducible but may be clustered around an erroneous value. We can measure the precision of a BGM or CGM by repeating measurements on the same blood sample or repeatedly measuring glucose using 2 or more CGM sensors simultaneously on the same subject. Even if the true value is not known, comparing the results for the multiple readings, we can derive a measure of precision.

For example, if 100 measurements gave a mean of 110 mg/dL with an SD of 5, the values would be very reproducible with a percentage error of about 5%. However, if the true value were actually 100 mg/dL, then these measurements would be biased and would be significantly inaccurate.

(*3*) Arithmetic deviation: If the true value is 100 mg/dL and the measured value is 110 mg/dL, then there is an arithmetic deviation of +10; similarly a value of 90 mg/dL would have an arithmetic deviation of −10.

For example, if the result of the meter or CGM being evaluated is 85 mg/dL, and the true value is 100 mg/dL (as provided by a very precise and accurate laboratory method or by some other reference method), then the arithmetic deviation is −15. These values can be calculated for each pair of true value and test-method value, and then averaged. The average should be extremely close to 0. One can then plot the arithmetic deviation versus the true value, to see if the average magnitude of the deviations varies systematically with the true value (Fig. 3) Bias is defined as a systematic (built-in) error, which makes all measured values wrong by a certain amount. As an overall estimate of bias, one can use the mean arithmetic deviation divided by the mean or average glucose level, expressed as a percentage (131,132).

(*4*) Absolute deviation: The absolute deviation is the absolute value of the arithmetic deviation. In the cases above, the absolute deviations of the arithmetic deviations +10 and −15 would be 10 and 15, respectively.

One should next examine the relationship of the absolute deviation and its average magnitude for various glucose ranges. There is almost always a systematic relationship between the absolute deviations and the true glucose level. If the true glucose level is not known, one can use the average value of multiple replicated measurements (Fig. 4).

(*5*) Absolute Relative Difference (ARD): Since an absolute deviation of 15 has a very different implication for a true value of 45 mg/dL compared with a true value of 400 mg/dL, it is common practice to express the absolute difference as a percentage of the true glucose. One can also plot ARD versus the true glucose levels as a continuous function (Fig. 5).

a. Mean Absolute Relative Difference (MARD): When we calculate an absolute relative deviation based on individual measurements using the meter

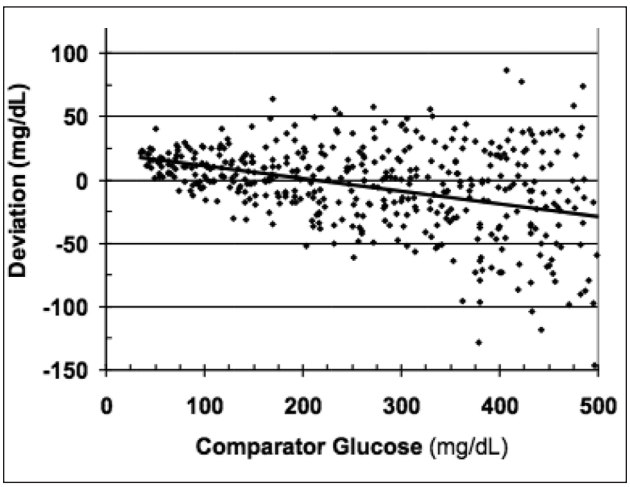


Fig. 3. Arithmetic deviations versus true glucose values (134). Relationship of deviations versus comparator glucose. The arithmetic (signed) deviations can vary in magnitude (bias) and in terms of their own variability depending on glucose level.

or CGM being evaluated (test method) as compared with a "true" laboratory-based method, there is a very large random sampling error. The mean absolute relative difference (MARD) is calculated as the average (mean) value of individual ARDs (133). To reduce the random sampling error in the measurement of ARD, it is desirable to calculate a MARD using a large number of paired test-comparator values for each specified narrow ranges of glucose (to achieve a 10% relative error in the MARD, it is necessary to have at least 500 data pairs).

MARD values have frequently been reported in the literature for the entire range of observed glucose levels (e.g., from 40 to 400 mg/dL). Since the ARD values differ systematically in the hypoglycemic, normoglycemic, and hyperglycemic ranges based on a specific GM device's performance, providing ARD data for narrow glucose ranges gives important and useful performance information (134). MARD values for CGM can vary systematically by day of wear (e.g., day 1 vs. day 3 vs. day 7) (Fig. 6) (135,136). MARD also depends on rate-of-change of glucose.

b. Median ARD: Rather than using MARD, some authors prefer to present results in terms of the median ARD.

One advantage of median ARD is that it is less influenced by outliers. However, it may be biased due to exclusion of the effects of outliers. Many studies have reported values for both MARD and the median ARD (frequently abbreviated as MedARD). MedARD is generally numerically smaller than MARD. The ratio of the MedARD to MARD has been found to be approximately 0.8 empirically for a variety of data in the literature. This is due to reduction in the influence of outliers, and the fact that the median is smaller than the mean for asymmetrical distributions such as ARD. It can be shown both empirically, using simulations, and theoretically, that the MedARD is approximately 0.8 MARD.

Table 6 summarizes the most commonly used terms that describe performance of glucose meters and sensors.

Understanding Clinical Standards for Accuracy of Current BGMs and CGMs

Error grids were the most popular early efforts to characterize the clinical significance of BGM device measurement errors. Regions of the grid are identified by letter designation, each reflecting the potential risk severity of incorrect treatment triggered by the measurement error (e.g., the device indicating hyperglycemia when someone is actually hypoglycemic). Clarke et al introduced the first error grid in 1987 (137). A variation of this grid was presented by Parkes et al in 2000 (Fig. 7) to smooth the boundaries of the grid regions. It incorporated the opinions of a greater number of expert clinicians (138). More recently, in 2014, a surveillance error grid with finer gradations in the categories for clinical error was introduced (139,140).

Device performance is typically reported as a percentage of glucose values in zone A or zones A + B (higher percentages in zone A or zones A + B indicate better performance). However, there are no generally accepted targets for clinical accuracy metrics such as percentage of observations within the various zones. These percentages may also depend on the range of blood glucose levels obtained. Error grids were a good tool to identify the frequency of egregious errors, but as meters have become more accurate, they are less useful for comparing device accuracy.

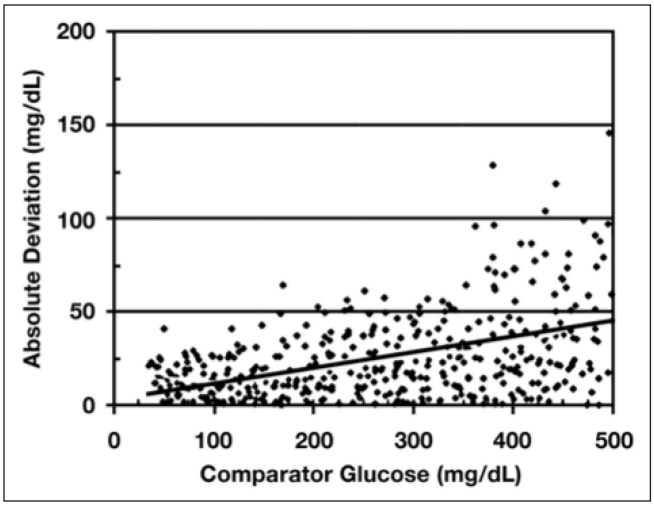


Fig. 4. Absolute difference: average magnitude of absolute deviations for various glucose levels (134). The absolute deviation of the test method from the comparator shows large random sampling variability. The magnitude of the absolute deviation and its own variability depend on glucose level. The least-squares regression line is shown.

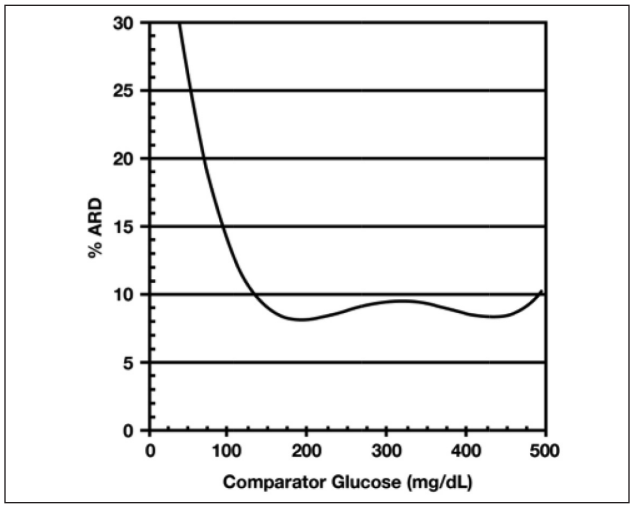


Fig. 5. Absolute relative deviation as a continuous function of true glucose (134).

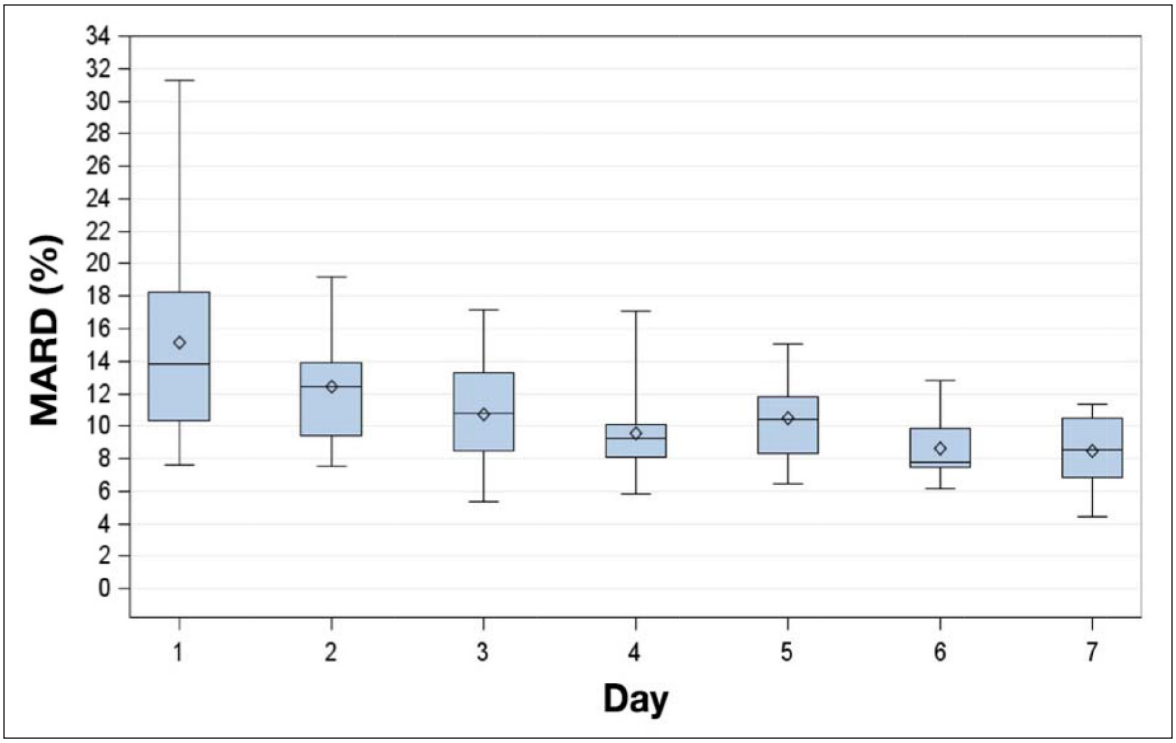


Fig. 6. CGM MARD values displayed by day of wear (135). Box plots for MARD on successive study days. Displayed are mean (diamonds), median (horizontal lines within boxes), 25th and 75th percentiles (lower and upper edge of the boxes), and minimum and maximum values (antennae). *CGM* = continuous glucose monitoring; *MARD* = mean absolute relative difference.

Linear regression and correlation is another common way of expressing device accuracy (Fig. 8). Bland-Altman plots are used to illustrate the magnitude of errors depending on the glucose level (Fig. 3) (134); these plots have been presented in a variety of formats. The vertical axis may show either arithmetic or relative error. The glucose levels shown on the horizontal scale may be the result of the comparator method or the average value of glucose measured by 2 methods subject to roughly comparable magnitude of error.

ISO Standards

In 2003 the ISO criteria for glucose meters were introduced; the FDA adopted these the following year. Official meter approval standards from 2003 to 2014 are summarized in Table 7 (122,123,131,141-143). The 2003 ISO 15197 standard requires that 95% of the values be accurate within ±15 mg/dL (0.83 mmol/L) for glucose values <75 mg/dL (4.2 mmol/L) and within ±20% for glucose values ≥75 mg/dL (4.2 mmol/L). These were updated in 2013 (ISO 15197-2013) to require 95% of values to be accurate within ±15 mg/dL (0.83 mmol/L) for glucose values <100 mg/dL (5.55 mmol/L) and within ±15% for glucose values ≥100 mg/dL (5.55 mmol/L) (131,142).

On January 7, 2014, the FDA released draft guidance for BGM accuracy that would require far more accuracy and precision from BGMs (143). The draft proposes that there be smaller errors in the hypoglycemic range and fewer outliers, allowing only 5% of measurements to have an error larger than ±15% and 1% of measurements to have an error greater ±20% above or below the reference value, rather than the 5% permitted under the 2003 ISO Guidelines. Further, the FDA was considering requesting that the experiment test be repeated 3 times, and the device would need to pass all 3 tests. This would make the testing more rigorous and conservative. If devices are tested by trained technicians, one would expect greater accuracy than if they were tested by untrained lay-persons such as patients and family caregivers. There is a suggestion that testing performed by nontrained people under "real-world" conditions might become required (144).

Not all BGMs that receive FDA approval provide the same degree of accuracy. Several published studies have compared BGM brands and models by name during head-to-head testing (56,57,136,145-148). For clinicians and consumers, MARD provides an excellent measure of accuracy and precision when evaluating a BGM (134). It has also been recommended that bias and coefficient of variation (%CV) should be reported (one can show mathematically and by simulations that there is a direct relationship between MARD and %CV: MARD is approximately 0.8 %CV) (132). The degree of BGM accuracy that is desired and required is likely to depend on the clinical needs of individual patients. There is a growing consensus among

Table 6
Common Terminology Related to GM Accuracy

Accuracy is defined as the closeness of agreement between a glucose test result and an accepted reference value. Accuracy improves when it has minimal bias and relative error (%CV, MARD, and minimal absolute error). Point accuracy refers to blood glucose values and sensor readings at single points in time (142,187).
Bias is an average of systematic error. It is measured as the difference or percentage difference of glucose values above (+) or below (–) reference values. The level of bias may differ systematically depending on the glucose level. The ideal bias is 0.0% (132,142).
Calibration for CGM refers to using periodic BGM measurements or a more accurate reference level from the laboratory, YSI device, or other measurement with higher accuracy to ensure accuracy. Devices and sensors vary in their requirements for frequency of calibration. Calibration of devices at the factory may eliminate the need for this step.
Percent coefficient of variation (%CV), defined as 100 × SD/(mean BG), expresses variability as the SD as a percentage of the mean glucose. This is a measure of the percentage error of repeated measurements of the same sample. The %CV usually varies systematically depending on glucose level.
Device stability is determined by the amount of change (also called drift) in accuracy over time (usually between the first and last measurement or between the first and second measurement). A commonly used stability standard is ≤4 mg/dL difference between measurements at BG concentrations ≤100 mg/dL or ≤4% at BG concentrations >100 mg/dL. Most current CGM devices require periodic recalibration to ensure accuracy over the life of the device (56,57,142,158).
Lag time refers to the difference in time between features (apices, nadirs) observed using capillary blood glucose as reflected in BGM or reference measurements and the time when the feature is observed using CGM (188).
Mean absolute relative deviation (MARD) is the most common measure used to characterize the accuracy of CGM but may also be used with BGM. MARD includes the effects of all outlier values.
Median absolute relative deviation (MedARD) is the median value of the absolute percentage deviation from reference glucose values. MedARD is less affected by outlier values than MARD. The MedARD is typically about 0.8 times the MARD.
Precision shows how closely a series of meter values agree with each other, regardless of how close they come to reference values. A GM that always reads 20% lower (or higher) than the true reference values may still have excellent precision. The precision of a device's readings is often measured as the %CV. High precision (repeatability) does not indicate accuracy.
Trend accuracy is a CGM device's ability to correctly measure the rate and direction of BG change over time (187).

Abbreviations: BG = blood glucose; BGM = blood glucose monitoring; CGM = continuous glucose monitoring; CV = coefficient of variation; GM = glucose monitoring; MARD = mean absolute relative deviation; SD = standard deviation; YSI = Yellow Springs Instruments.

endocrinologists and other clinicians that the accuracy and precision performance characteristics of each BGM and CGM device should be made available both to the patient and physician, to properly match a BGM device to the appropriate individual or clinical setting (149).

How Much Accuracy Is Needed?

Research on the impact of GM inaccuracy on health outcomes is limited; however, computer modeling can separate the impact of GM errors on glucose outcomes from those due to other factors. Modeling studies indicate that patients receiving bolus insulin therapy face increased risk of hypoglycemia even when using GM devices that achieve current standards (140,150-153).

One study used 100 simulated adults with T1DM to run 16,000 virtual trials applying varying levels of simulated BGM error (5%, 10%, 15%, and 20% deviation from true blood glucose values). Results showed that glycemic control deteriorated with each increase in BGM error. Failure to detect hypoglycemic episodes, hypoglycemia risk, glycemic variability, and A1C increased as BGM error level increased (150). In another study, Schnell and colleagues reported that improvements in BGM accuracy (reducing error from ±20 to ±5%) would be expected to result in a 10% reduction in severe hypoglycemia, a 0.4% reduction in A1C levels, and a 0.5% relative reduction in myocardial infarction. This study (2012 data) estimated an annual cost savings from this kind of improvement in BGM accuracy of €9.4 million for patients with T1DM and €55.5 million for insulin-treated patients with T2DM for Germany alone (151).

Another study of 100 simulated cases being treated with intravenous insulin therapy in an intensive care setting found that increases in either BGM imprecision

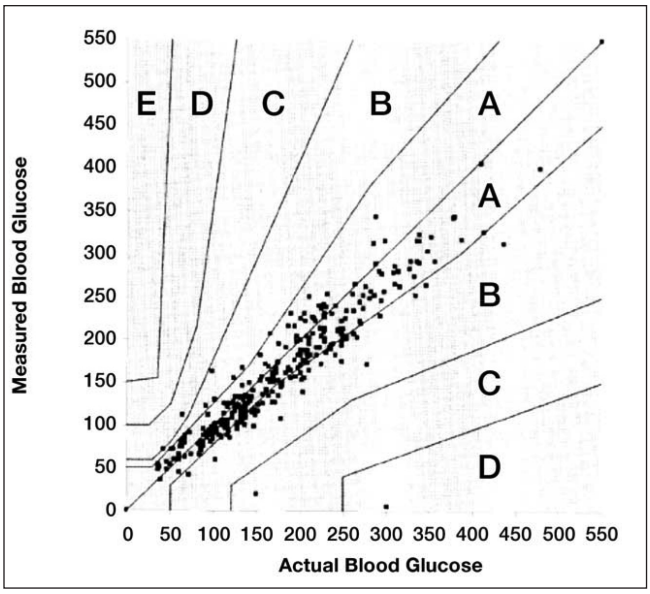


Fig. 7. Parkes error grid (138).

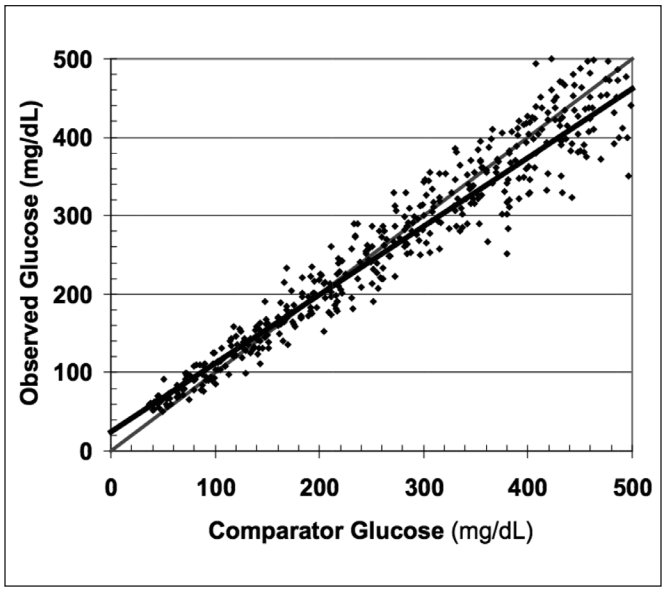


Fig. 8. Linear regression relationship between observed and comparator glucose (134).

(measured as %CV) or bias, tested separately (with 1 or the other variable set to 0), increased glucose variability and the frequency of hypoglycemia and hyperglycemia (154). BGMs with a %CV ≤6.5% and bias ≤5% rarely lead to major (2-step or greater) errors in insulin dosing. This degree of accuracy would ensure that the rate of any insulin dosing errors would be <5% (155). Table 8 summarizes clinical situations where increased accuracy may be of particular benefit.

What Impacts Accuracy?

Manufacturing defects and test-strip lot-to-lot variations directly impact accuracy and introduce bias (156,157). Bias is typically measured in the hypoglycemic range, target range, and hyperglycemic range. One study of test-strip accuracy compared 7 meters and tested 3 test-strip lots for each range and found that lot-to-lot variations were as high as 11% using the same meter (158). Another study found that the difference in bias between widely used BGM devices was as high as 4.8% (159). Underfilling the test strip can introduce errors >20% in some BGMs. In another study, only 5 of 31 glucose meters were able to maintain 100% accuracy (either giving the correct reading or rejecting the reading appropriately) when test strips were deliberately underfilled (160).

Although many meters have been approved for alternate site testing (e.g., sampling from the palm, upper arm, forearm, thigh or calf, rather than the fingertip), this practice can generate inaccurate results, particularly when glucose levels are changing rapidly such as after meals or after exercise, when the patient is ill or under stress, or shortly after insulin administration (68).

BGM testing methods are predominately based on the glucose oxidase or glucose-1-dehydrogenase enzyme. Any factor that interferes or impacts these enzymes or the BGM itself can degrade overall accuracy. Variation can be due to issues such as competing blood substrates (e.g., maltose, vitamin C) (161,162), environmental issues (e.g., cold temperature, high altitude with reduced oxygen pressure), and factors related to individual patients. Reduced accuracy and precision have been observed in tests performed by patients and other lay users compared with highly trained, experienced health professionals (163). GM accuracy is just one of many factors influencing the quality of subsequent glycemic control achieved. Contaminants on the skin from food sources (fruits, juices, sodas, milk) and even hand lotions can artificially raise capillary blood glucose levels and potentially lead to an overdose of insulin with subsequent hypoglycemia. Acetaminophen is well-known to result in spurious values in CGM systems (15,44,56,164,165). Physical compression of the CGM sensor during sleep can result in seriously low glucose readings.

How to Communicate Device Accuracy Data

It would be highly desirable to be able to label each GM device and its test strips or sensors with their performance characteristics, and methods for labeling have been contemplated for several years (166,167). In a recent guidance document (143), the FDA suggests a simple system that shows the percentage of a BGM glucose values expected to fall within 5%, 10%, 15%, and 20% of the reference values (Fig. 9) (143). This allows clinicians and patients more insight into the accuracy of a particular GM device so they can make an informed choice.

Table 7
Prior, Current, and Proposed Glucose Meter Performance Recommendations and Standards (131,142,143)

Meter approval standards			
ISO 15197 2003 (adopted by FDA 2004)	<75 mg/dL (<4.2 mmol/L)	±15 mg/dL (±0.83 mmol/L)	95%[a]
	≥75 mg/dL (≥4.2 mmol/L)	±20%	
ISO 15197 2013	<100 mg/dL (<5.55 mmol/L)	±15 mg/dL (±0.83 mmol/L)	95%[a,b]
	≥100 mg/dL (≥5.55 mmol/L)	±15%	
FDA 2014	50-400 mg/dL (2.8-22.2 mmol/L)	±15%	95%
	AND		
	50-400 mg/dL (2.8-22.2 mmol/l)	±20%	99%

Abbreviations: ADA = American Diabetes Association; FDA = US Food and Drug Administration; ISO = International Organization for Standardization.
[a] Both FDA and ISO standards allow 5% of meter values to be outside these limits. There was no limitation on the clinical severity of these outliers prior to 2013.
[b] 99% of values must be within Consensus Error Grid (138) zones A or B.

BGM Accuracy Is Necessary but not Sufficient to Improve Quality of Glycemic Control

As measurement tools, BGMs and CGMs generate data used to make treatment decisions and adjust diabetes medication doses. The aptitude of patients and clinicians with regard to data analysis and interpretation varies widely. Accordingly, the methods of data display and reporting are critically important. Older BGMs displayed a single value without context. In contrast, many current BGMs report weekly or monthly averages for glucose and may also highlight patterns in glycemic variability (e.g., consistently high or low values at a particular time of day or in relationship to a specified meal). Similarly, current CGM devices have on-screen analysis capabilities that display glucose trend lines over time, with arrows reflecting the magnitude of the current rate-of-change of glucose. These features provide additional information and help give context to raw glucose numbers. However, many users will require guidance to effectively use these informative features.

Clinicians should also consider the ease and speed of BGM downloading to ensure that the end user will be able to identify glucose patterns and that clinical interventions will be properly implemented. Currently, each device has proprietary software that displays data in widely differing formats, making clinical interpretation difficult. To accommodate their patients, clinicians need to master multiple software products. Although no current software downloads every device, several companies and organizations are attempting to develop standardized methods to download and display data from nearly every type of BGM, CGM, insulin pump, and other health devices (e.g., activity monitors).

To correctly gauge the timing of hypoglycemic and hyperglycemic events, the clock setting in the BGM must be accurate (168). BGM clock settings should be clearly visible and easy to adjust and should remain accurate when a battery is changed or temporarily removed. Clocks in the meter, CGM, and insulin pump (if utilized) should be synchronized (automatically if possible), with accommodation for travel across time zones. Ideally, all glucose and related data should be integrated with an electronic health record.

It has been proposed that the ongoing routine quality assurance verification currently being performed by manufacturers to ensure the accuracy and precision of subsequent lots of test strips should be confirmed by independent laboratories using a standardized methodology (146). In support of this concept, Freckmann and colleagues reviewed the accuracy of 27 meters previously approved in Europe under the 2003 ISO 15197 standard (±20% for glucose levels >75 mg/dL and ±15 mg/dL for glucose levels ≤75 mg/dL). In postapproval testing, more than 40% of the meters failed to meet the standard by which they had previously received approval (58). When people with diabetes

Table 8
Clinical Situations That May Require Greater Glucose Monitoring Accuracy

Patients requiring the highest possible accuracy in glucose monitoring
• History of severe hypoglycemia
• Hypoglycemia unawareness
• Pregnancy
• Infants and children receiving insulin therapy
• Patients at risk for hypoglycemia, including:
o Patients receiving basal insulin
o Patients receiving basal bolus inulin therapy with multiple injections per day
o Patients receiving sulfonylureas or glinides (insulin secretagogues)
o Patients with irregular schedules, skipped or small meals, vigorous exercise, travel between time zones, disrupted sleep schedules, shift work
• People with occupational risks that enhance possible risks from hypoglycemia (for example, involving driving or operating hazardous machinery)

Your ABC meter result may vary slightly from your actual blood glucose value. This may be due to slight differences in technique and the natural variation in the testing technology.

The chart below shows the results of a study where 350 typical users used the ABC meter to test their blood glucose levels. For example, in this study, the ABC meter gave results within 15% of their true blood glucose level 340 out of 350 times.

Difference in range between the true blood glucose level and the ABC meter result	Within 5%	Within 10%	Within 15%	Within 20%
The percent (and number) of meter results that match true blood glucose level with x%	57% (200/350)	94% (330/350)	97% (340/350)	100% (350/350)

Accuracy Levels	**Meter Results Meeting Standard**	**Percentage of meter values compared to laboratory values**
Accurate	350 out of 350	±15%
More Accurate	262 out of 350	±10%
Most Accurate	175 out of 350	±5%

Fig. 9. Sample label information for meter and test-strip boxes (From the US Food and Drug Administration Guidance Document) (143).

performed the testing, fully one-third of meters failed to meet the 2003 ISO 15197 standards (169). A recent study showed that only 12 (44.4%) of 27 available BGMs met the most recent 2013 ISO 15197 standard. Only 13 of 27 (48.1%) BGMs gave adequately accurate results in the hypoglycemic range, while 19 (70.3%) had sufficient accuracy for glucose levels >250 mg/dL (13.9 mmol/L) (170). Unfortunately, one cannot assume that FDA approval implies that a BGM will continue to meet FDA accuracy requirements for subsequent batches of test strips.

Glucometrics, Downloading, and Interpretation of GM Data

The analysis and display of glucose data is termed "glucometrics" (171). It can describe the average value, distribution of glucose, glucose variability, patterns during the day and night, effects of days of the week, and long-term trends. The availability of GM devices with electronic memory and the ability to download these data has fueled the rapidly growing science of glucometrics. Retrospective analysis of glucose levels, both overall and at specific times (e.g., after major meals or on selected days of the week), can provide insights into how factors such as medications, diet, stress, and activity contribute to diabetes control and how those factors should be addressed or adjusted (82,172). Communication of glucometric data to the healthcare team is key; communication methods between patient and clinician are presented in Table 3.

Which glucometrics parameters are best? Approaches vary in complexity but usually generate similar types of information (171,173). With enough information, it becomes possible to evaluate whether the A1C level, still the gold standard, is consistent with the patient's average blood glucose (174).

Table 9 summarizes high-level, clinically relevant information that can be obtained from BGM or CGM data. Either the mean or median can be used to characterize the average glucose level. Since the SD of glucose is fairly highly correlated with the mean glucose, %CV is usually the best single simple method to characterize variability (26,37,175-178). As an approximation, SD tends to be higher in patients with higher mean glucose values. While mean, median, and %CV metrics describe overall glycemia, several additional methods have been developed to describe actionable patterns to help clinicians optimize diabetes therapy. In a graphical presentation, the "standard day," "modal day," (179,180) or ambulatory glucose profile (AGP) displays individual glucose measurements (pooled over multiple days) by time of day on a single 24-hour scale (Table 9; image 1*A*; image 1*B*.; image 2*A*.). This graph indicates both the glucose values and the times of day when people have been monitoring their glucose levels, facilitating the detection of any consistent patterns in glucose excursions and providing an assessment of the adequacy of GM. The "Standard Day" is simple in principle but can be difficult to interpret in view of the large amount of scatter observed in glucose data obtained over several days.

AGP

The AGP was introduced by Mazze et al (1987) for BGM and subsequently applied with further enhancements (display of the smoothed curves for the 10th and 90th percentiles) to CGM data by Mazze (2008) and Bergenstal and colleagues (2013). The AGP provides an excellent starting point for a standardized computerized display of BGM and/or CGM data by time of day (173,178,179). To generate the AGP, an individual's blood glucose levels are measured via CGM or BGM with all glucose data pooled and analyzed as if it had been collected during a single 24-hour period. The result is a standardized software report that can be displayed graphically. Examples of graphic AGP displays for patients with normal glucose tolerance, T1DM, and T2DM are shown in Table 9 (images 2*A*-*C*) (173,181). AGP has been proposed as a standardized method for glucose reporting and analysis (173,178,181). One can also examine these 24-hour patterns in glucose by day of the week (180). It is customary to report a number of statistics to accompany the graphical display of the AGP (173).

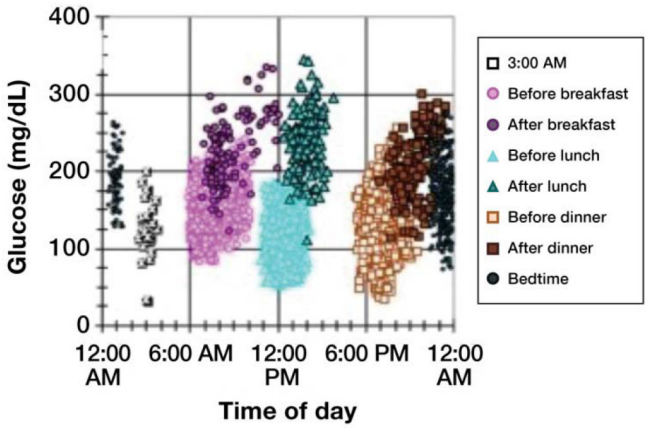
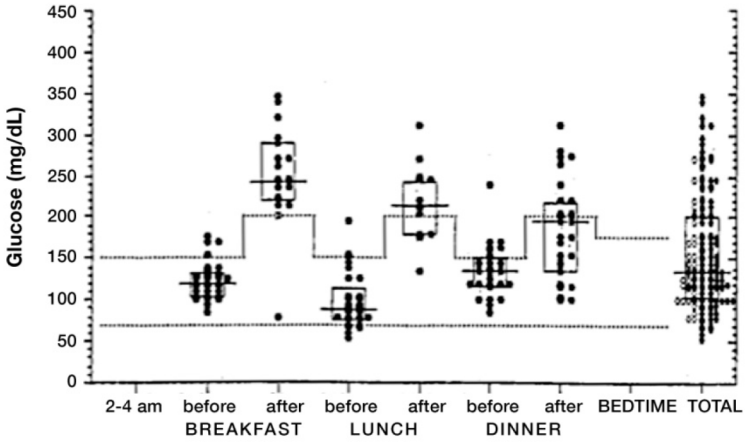
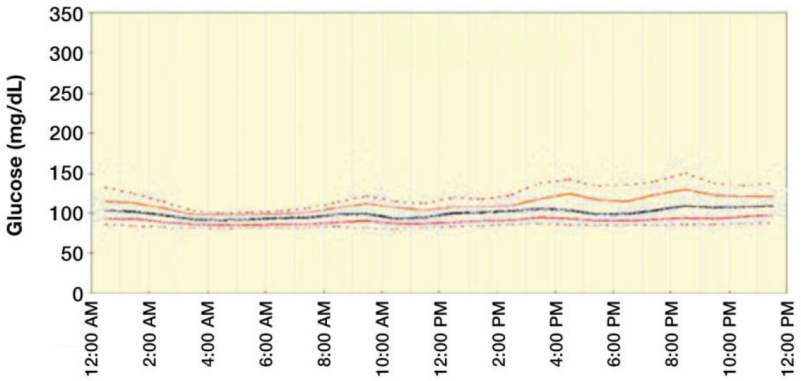
Several additional graphic displays of data related to changes in glucose over time, time within different glucose ranges, glucose profile, etc. are shown in Table 9. Some are simplistic (e.g., pie graphs or simple bar charts displaying percentages of glucose values above, below, and within the target range). Others are slightly more complex (e.g., box plots [a methodology introduced by Tukey as part of his approach to Exploratory Data Analysis that makes no assumptions about the nature of the underlying distribution of glucose values and was introduced into glucometrics by Rodbard (180,182)], scattergrams, stacked bar charts, and histograms). Their purpose is to help the clinician identify and prioritize clinical problems and then educate and motivate the patient to achieve improved glycemic control.

Recommendations

Health professionals should educate patients regarding the interpretation and use of GM data to help modify patient behaviors, enhance their ability to self-adjust therapy, and help them decide when to seek medical assistance.

To assess glucometrics, first examine the overall statistics (mean, SD, %CV); distribution of glucose values (e.g., stacked bar charts); and glucose by date, time of day, in relationship to meals, and by day of the week. This document provides several examples for each of these types of analyses. Usually, the most helpful are graphs of glucose by date, the AGP by time of day, stacked bar charts in relationship to time of day, and stacked bar charts and "box plots" for glucose in relation to meals and by day of the week.

Table 9
Glucometrics: Key Characteristics of BGM and CGM Glucose Data (171,173,174,179,181,182, 190)

Average glucose	
Mean, median Calculated value of A1C corresponding to the observed average glucose	
Glucose variability	
SD, %CV, IQR, maximum, minimum, range	
Standard/modal day	
1*A*. Glucose profile by time of day	
1*B*. Glucose values shown in relation to meals (solid circles) superimposed on target ranges for preprandial and postprandial glucose. Horizontal lines: median. The rectangles show the 25th and 75th percentiles.	
AGP	
2*A*. Patient with normal glucose tolerance (example) Ambulatory glucose profile (AGP) for CGM data (typically using data from 14 days), with smoothed estimates of 10th, 25th, 50th, 75th, and 90th percentiles	

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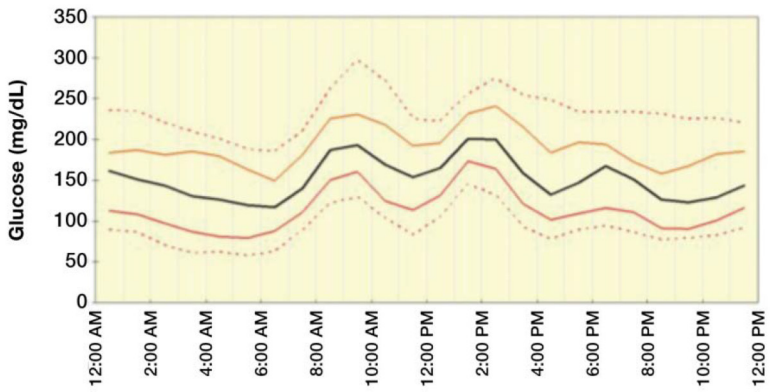
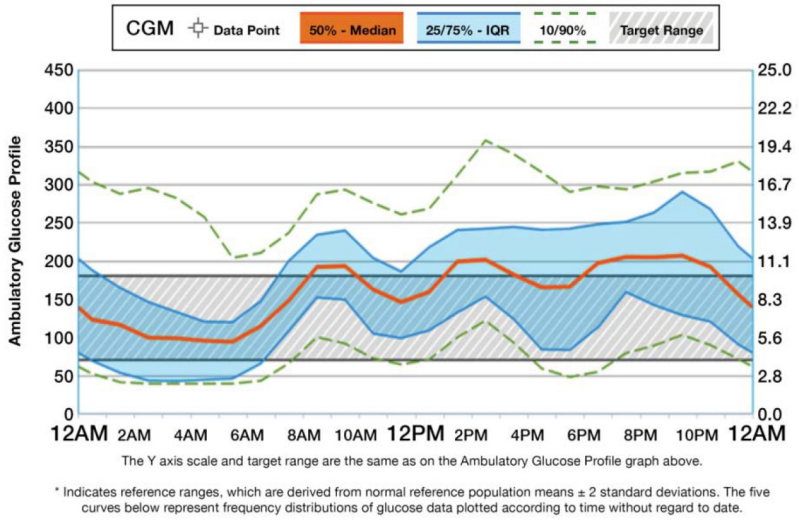
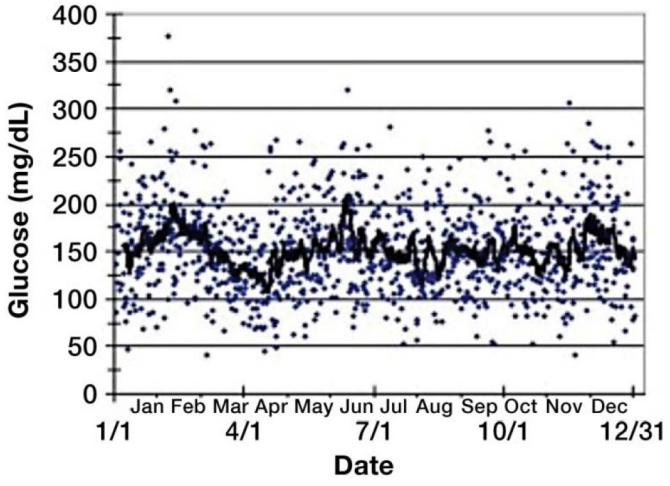
2*B*. Patient with T1DM (example)	
2*C*. Patient with T2DM The solid curve in the middle represents the smoothed median glucose (50th percentile) values for a 24-hour period. The blue shaded area around the median reflects the range between the 25th and 75th percentiles, which includes 50% of the patient's glucose readings for any specified time of day. The average vertical distance between the shaded curves is the overall IQR. The dashed lines show smoothed 10th and 90th percentiles. The striped, shaded area shows the presumptive target range (70-180 mg/dL or 3.9-10 mmol/L).	
Change in glucose over time	
3. Glucose by *date* for all glucose values. May also be used for: • Mean glucose • Fasting glucose • Glucose values at any selected time of day	

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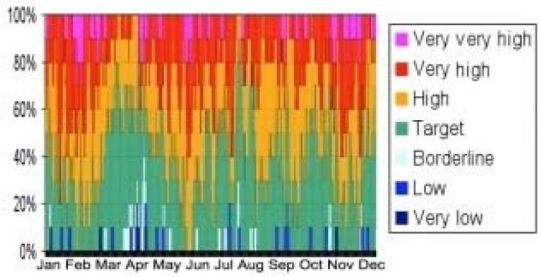
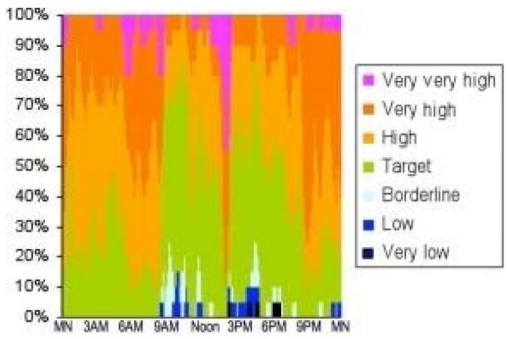
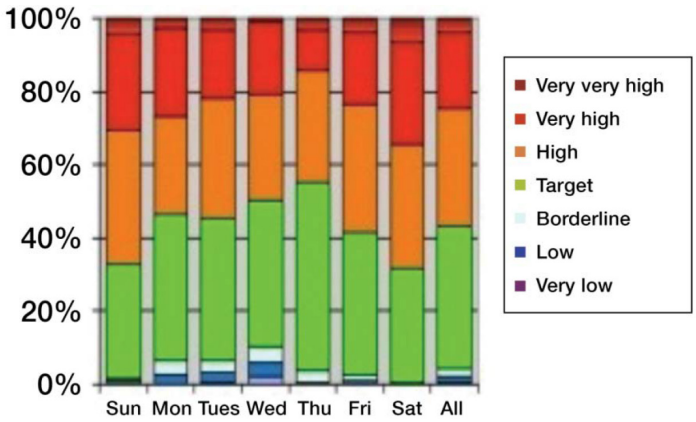
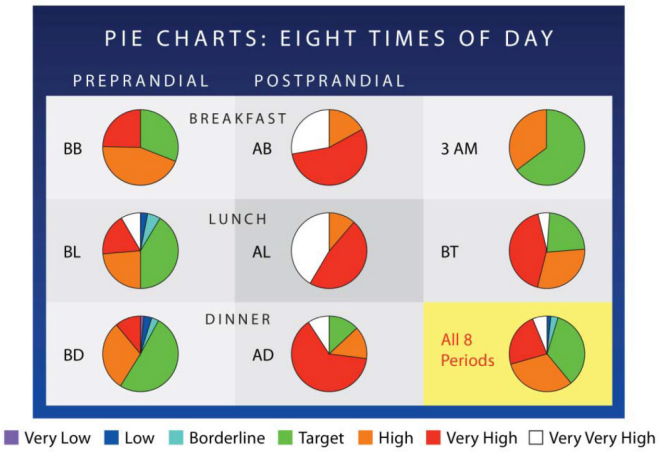
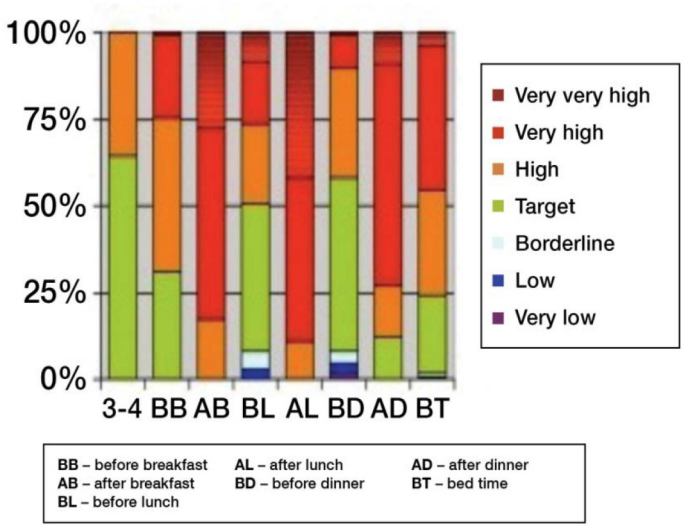
4. Percentage of time in 7 categories, by date, for 1 year	
Glucose distribution	
Quality of glycemic control	
5. Percentage of values in multiple categories of glycemic quality by time of day • Percentage in target range (green) • Percentage hyperglycemia (orange, dark orange, or pink, representing different degrees of severity) • Percentage hypoglycemia (light blue, dark blue, blue-black)	
6. Categories of glycemic quality by day of the week (using stacked bar charts with 7 glucose level categories)	
7. Proportion of glucose values within the hypoglycemic, target, and hyperglycemic ranges in relationship to meals 7*A*. Pie charts showing before and after meals, at bedtime, and overnight (3 AM)	

(Continued next page)

7*B*. Proportion of glucose values within the hypoglycemic, target, and hyperglycemic ranges in relationship to meals (stacked bar charts)



Integration with other relevant "logbook" data

8. Medications, insulin doses, diet, physical activity/exercise, illness, stress, travel

8.9 Enhanced Logbook		Breakfast		Lunch		Dinner		Night	
		Before	After	Before	After	Before	After	Bedtime	2 a.m.
Sun ___/___/___ Notes:	BG								
	Time								
	Carbs								
	Bolus								
Mon ___/___/___	BG								
	Time								
	Carbs								
	Bolus								
Tue ___/___/___	BG								
	Time								
	Carbs								
	Bolus								

Abbreviations: AB = after breakfast; AD = after dinner; AGP = ambulatory glucose profile; A1C = glycated hemoglobin; AL = after lunch; BB = before breakfast; BD = before dinner; BG = blood glucose; BGM = blood glucose monitoring; BL = before lunch; BT = bedtime; CGM = continuous glucose monitoring; CV = coefficient of variation; IQR = interquartile range; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Image citations: 1A, 3, 4, 5, 6, 7A, 7B: Rodbard D, et al. J Diabetes Sci Technol. 2009;3:1388-1394.; 1B.: Pernick N and Rodbard D. Diabetes Care. 1986;9:61-69.; 2. A., 2. B.: Mazze RS, et al. Diabetes Technol Ther. 2008;10:149-159.; 2C.: Bergenstal R, et al. J Diabetes Sci Technol. 2013;7:562-578.; 8: Walsh J, et al. Using Insulin: Everything You Need for Success with Insulin. San Diego, CA: Torrey Pines Press. 2003.

Persons with diabetes who use an insulin pump have a rich data set of additional information to supplement glucose values that includes the time and amount of all insulin administered whether for a meal or for a correction, as well as all recorded carbohydrate intake. Nonpump users must track insulin use manually. A review of reports that include medication history can greatly improve one's ability to make therapeutic decisions and advise the patient.

CONCLUSION

GM is an essential component of care for all patients with diabetes. Over the years, BGM meters and CGM sensors have improved dramatically in terms of accuracy, data usefulness, and the availability of automated analyses and interpretation. This document seeks to encourage "meaningful monitoring," a term that signifies an approach that

is intended to empower patients to manage glucose levels and reduce the risk of hypoglycemia. Meaningful monitoring will likely be different for each individual. Clinical practice guidelines from all major diabetes organizations recommend routine BGM for patients with T1DM. Most of these guidelines also recommend CGM for patients with a history of severe hypoglycemia or hypoglycemia unawareness, as well as for patients not at goal based on A1C. Many pediatric patients with T1DM are candidates for CGM, especially if they and their family caregivers have the appropriate training to use the information effectively.

Meaningful monitoring in patients with T2DM should also be individualized depending on the risk of hypoglycemia estimated based on prior history, presence of hypoglycemia unawareness, and the nature of the current therapy (e.g., whether the patient is receiving medications with relatively high hypoglycemia risk, such as insulin, sulfonylureas, or glinides). There have been some studies of CGM in T2DM, but more trials are needed to identify the settings in which it can be most beneficial and cost-effective. In T2DM as in T1DM, CGM can be useful in patients with unappreciated hyperglycemia, as well as in patients who are at high risk for hypoglycemia, those who have hypoglycemia unawareness, and those using intensive insulin therapy (44).

Patients and clinicians should be educated to understand and use GM data. Glucometric data analysis can help both patients and clinicians assess the quality of glycemic control, identify glucose patterns and responses to therapy, and evaluate glucose variability. Glucometric analysis can also be used as an educational tool. Education is essential to making apparent the relationship of specific glucose data with medication and other therapeutic interventions.

Looking forward, one can expect increased BGM accuracy and the continuing rapid evolution of CGM devices. Many improvements are in progress, including data sharing via the Internet (e.g., as implemented by Nightscout, Dexcom Share, Medtronic), use of additional displays (e.g., Apple Watch™), increased duration of use, and improved usability (size, weight, form factor, ease of insertion, ease of interface with other devices, options for placement site). Several mobile-health applications have been developed for mobile phones, enabling patients to monitor and adjust their lifestyle and therapy on a continuing real-time basis. As the technology advances, there is a vital need to integrate the multiple data inputs from insulin pumps, glucose sensors, glucose meters, and carbohydrate intake in a comprehensive and standardized way so clinicians and patients can make sense of it all.

Additionally, CGM devices are now available with a longer duration of use (2 weeks); others in development may be implanted and last 6 months or longer. Some devices are factory calibrated and do not require additional calibrations by the end user. Devices will become smaller, lighter, and simpler to use. Some will have fewer features (e.g., no alarms), while others may have additional features and will integrate with insulin delivery (e.g., "artificial pancreas") systems. These are examples of device innovations that may broaden the appeal and applicability of CGM both in T1DM and T2DM. New clinical trials will be needed to better understand how to optimally utilize this technology for various patient populations with T2DM.

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Medical Writer

Ms. Caitlin Rothermel has no multiplicity of interest to disclose.

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CONTINUOUS GLUCOSE MONITORING: A CONSENSUS CONFERENCE OF THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY

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This document represents the position of the American Association of Clinical Endocrinologists and the American College of Endocrinology Consensus Conference Writing Committee. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position and consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

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ABSTRACT

Objective/Methods: Barriers to continuous glucose monitoring (CGM) use continue to hamper adoption of this valuable technology for the management of diabetes. The American Association of Clinical Endocrinologists and the American College of Endocrinology convened a public consensus conference February 20, 2016, to review available CGM data and propose strategies for expanding CGM access.

Results: Conference participants agreed that evidence supports the benefits of CGM in type 1 diabetes and that these benefits are likely to apply whenever intensive insulin therapy is used, regardless of diabetes type. CGM is likely to reduce healthcare resource utilization for acute and chronic complications, although real-world analyses are needed to confirm potential cost savings and quality of life improvements. Ongoing technological advances have improved CGM accuracy and usability, but more innovations in human factors, data delivery, reporting, and interpretation are needed to foster expanded use. The development of a standardized data report using similar metrics across all devices would facilitate clinician and patient understanding and utilization of CGM. Expanded CGM coverage by government and private payers is an urgent need.

Conclusion: CGM improves glycemic control, reduces hypoglycemia, and may reduce overall costs of diabetes management. Expanding CGM coverage and utilization is likely to improve the health outcomes of people with diabetes. **(Endocr Pract. 2016;22:1008-1021)**

Abbreviations:
A1C = glycated hemoglobin; **AACE** = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **ASPIRE** = Automation to Simulate Pancreatic Insulin Response; **CGM** = continuous glucose monitoring; **HRQOL** = health-related quality of life; **ICER** = incremental cost-effectiveness ratio; **JDRF** = Juvenile Diabetes Research Foundation; **MARD** = mean absolute relative difference; **MDI** = multiple daily injections; **QALY** = quality-adjusted life years; **RCT** = randomized, controlled trial; **SAP** = sensor-augmented pump; **SMBG** = self-monitoring of blood glucose; **STAR** = Sensor-Augmented Pump Therapy for A1C Reduction; **T1D** = type 1 diabetes; **T2D** = type 2 diabetes

EXECUTIVE SUMMARY

Continuous glucose monitoring (CGM) has been commercially available since the early 2000s but has not been widely adopted in the management of diabetes. In light of advances in CGM technology and a growing body of evidence supporting CGM benefits, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) convened a public consensus conference February 20, 2016, to review available CGM data and develop strategies for overcoming barriers to CGM use and access (see Appendix for agenda and participants). Representatives from medical and scientific societies, patient advocacy organizations, government, health insurance providers, and device and pharmaceutical manufacturers met to discuss 4 key questions related to CGM use (Table 1). A detailed report on the scientific evidence supporting the consensus conference's conclusions follows this summary.

Question 1. How would patients, clinicians, and payers benefit from expanded use of personal and professional CGM?

- Extensive data from randomized controlled and other trials support the use of CGM in children and adults with type 1 diabetes (T1D). CGM may have similar benefits in insulin-using patients with type 2 diabetes (T2D) and pregnant women with diabetes.
- Advances in CGM technology have improved the accuracy and reliability of these devices.
- CGM is likely to reduce costs associated with hypoglycemia and severe hyperglycemia by alerting patients to impending or actual low or high glucose values and thereby facilitating prompt action and prevention of hospitalizations. CGM use may also reduce healthcare costs due to chronic diabetes complications, although more studies of the economic impact of CGM are needed.

Question 2. What CGM data are relevant and how should they be reported?

- The primary display of all CGM devices should highlight actionable data, such as:
  - Current glucose level
  - Glucose trend arrows
  - Graphs showing glucose trends over past day
- The default trigger for hypoglycemia alerts should be <70 mg/dL, which matches the generally agreed upon threshold for hypoglycemia and also allows for a window of safety to compensate for potential disparities between the CGM measurement of interstitial glucose and blood glucose values. Additional alerts at other modifiable trigger values may be useful.
- The downloadable report of all CGM devices should include a standardized report that includes such metrics as time in range, glycemic variability, patterns of hypoglycemia and hyperglycemia, and other customizable parameters deemed essential by the clinician and patient.

- CGM data should be evaluated in context with other variables such as meals, treatments, exercise, illness, insulin boluses, and automated insulin delivery activity.
- Standardized metrics and reporting among available CGM devices would facilitate understanding by patients and clinicians and promote wider adoption of CGM technology.
- Automated, rapid access to CGM data is essential for utilization by clinicians and useful for patients.

Question 3. How should the data and reporting be interpreted?

- Whether CGM is used intermittently or continuously, patients should generally be able to see and react to glucose data. However, CGM without data display (i.e., masked CGM) may be beneficial when used intermittently with advice and supervision from clinicians. Masked CGM can also serve as an important outcome measure for clinical trials in diabetes.
- CGM reports should be interpreted by trained clinicians but should include summary reports designed to be understood by patients.
- CGM training for clinicians should be made widely available to all involved in diabetes management and should encompass the use and interpretation of CGM data as well as the delivery of CGM patient education. CGM certification should not be required, as this would add another barrier and hinder wider adoption of CGM technology.

Question 4.1. What clinical data are currently available to support expanded CGM coverage by payers as pertains to questions 1 and 3?

- Data consistently support CGM-associated improvements in glycated hemoglobin (A1C) and reduced risk of hypoglycemia in patients using intensive insulin therapy for T1D.

Question 4.2. What additional data are needed?

- CGM is likely to provide significant benefits to the following patient populations, although additional studies are needed:
  - Patients older than 65 years with comorbidities and/or at risk for severe hypoglycemia
  - Women with diabetes who are or are planning to become pregnant as well as women with gestational diabetes
  - Patients with kidney disease
  - Patients with diagnosed hypoglycemia unawareness
- Cost-effectiveness studies are needed to further document healthcare cost reductions associated with CGM.

Call for Action

- Reimbursement should be expanded to cover clinician time spent reviewing and interpreting CGM data and advising patients outside of as well as during patient visits.
- Advancements in data delivery and interpretation through cloud-connected devices, electronic medical records, standardized reports, and other improvements are needed to increase clinician efficiency in reviewing and interpreting CGM data, facilitating better patient care and outcomes.

INTRODUCTION

CGM consists of a subcutaneously inserted sensor that measures interstitial glucose and delivers glucose values to a recording device. Most devices have a real-time display and other features that permit patients to respond to changing glucose values, and all can generate reports for later analysis. CGM use facilitates modest improvements in glucose control as measured by A1C without increasing, and sometimes reducing, the risk of hypoglycemia, thus facilitating safer intensification of glucose control. Technological advancements have also improved the accuracy and wearability (comfort, size, data display, fit, etc.) of these devices. However, CGM has been used on a regular basis by only a small minority of patients with diabetes: about 15% of T1D patients and even fewer with T2D (1). In February 2016, the AACE and ACE convened a public consensus conference to examine the evidence supporting CGM and the barriers to its adoption. Representatives from medical and scientific societies, patient advocacy organiza-

Table 1
Pillar Questions

1. How would patients, clinicians, and payers benefit from expanded use of personal and professional CGM?
2. What CGM data are relevant and how should they be reported?
3. How should the data and reporting be interpreted?
4. What clinical data are currently available to support expanded CGM coverage by payers as pertains to questions 1 and 3? What additional data are needed?

Abbreviation: CGM = continuous glucose monitoring.

tions, government, health insurance providers, and device and pharmaceutical manufacturers met to discuss 4 key questions related to CGM use. Each question was divided into 4 to 5 subquestions, as detailed below.

In this document, *professional use* refers to CGM devices owned by the clinician's office and used intermittently to assess glycemic patterns for therapeutic decision-making, whereas *personal use* refers to CGM devices owned by patients who use it for making real-time and retrospective adjustments to diabetes management. *Masked CGM* refers to professional devices without a data display, which may be used intermittently in conjunction with advice from clinicians or in clinical trials to clarify the action and evaluate the efficacy and safety of investigational medications. The CGM Consensus Conference Writing Committee acknowledges the limitations of CGM, including variable accuracy in the first hours of sensor use, the lead-lag phenomenon that occurs with rapid glucose changes and that contributes to differences between CGM readings and self-monitoring of blood glucose (SMBG) results, and larger mean absolute relative differences (MARDs; a measure of the average disparity between the CGM measurement and a reference blood glucose measurement) occurring in the hypoglycemic range. These concerns have been described in detail elsewhere (2-4).

Question 1. How would patients, clinicians, and payers benefit from expanded use of personal and professional CGM?

Question 1.1. What data support the use of CGM for either personal or professional use?

Personal use of real-time CGM on a frequent basis in children and adults with T1D is strongly supported by evidence from randomized, controlled trials (RCTs; e.g., Juvenile Diabetes Research Foundation [JDRF] CGM Study, the Sensor-Augmented Pump Therapy for A1C Reduction [STAR] 3 study, and the Automation to Simulate Pancreatic Insulin Response [ASPIRE] study), as well as observational data from the Type 1 Diabetes Exchange (T1D Exchange) clinic registry.

Conducted in 2007, the JDRF CGM trial included 322 adults and children with T1D and was designed to compare use of a CGM device (DexCom Seven™ [DexCom, San Diego, CA], the MiniMed Paradigm Real-Time Insulin Pump and Continuous Glucose Monitoring System [Medtronic, Minneapolis, MN], or the FreeStyle Navigator™ [Abbott Diabetes Care, Alameda, CA], chosen according to investigator/patient preference) with traditional SMBG using meters and test strips (5). Study results demonstrated that using CGM >6 times per week reduced mean hemoglobin A1C by 0.5 to 0.8% across all age groups from a mean baseline A1C of 7.6 to 8.0% without an increased incidence of severe hypoglycemia (5-9). CGM users with baseline A1C levels <7.0% maintained A1C values between 6.4 and 6.5% and also experienced a 33 to 50% reduction in sensor values <70 mg/dL compared to patients in the control group. In the low baseline A1C cohort, the control group experienced significantly increased A1C levels (9,10).

In the STAR3 Study (conducted in 2007-2008), T1D patients were randomly assigned to therapy with a sensor-augmented pump (SAP) device that integrated an insulin pump with CGM (MiniMed Paradigm REAL-Time System™ [Medtronic]) or multiple daily injections (MDI) of insulin plus SMBG. A1C in children and adults using the SAP device decreased by 0.8%, with a net difference of 0.6% relative to the MDI+SMBG control group. Hypoglycemia rates were similar in the 2 groups (11). Similar results were seen across age groups, and the benefits increased with increasing frequency of CGM use (11-13). An observational study using data from the Medtronic CareLink database showed that patients who used CGM with an insulin pump ≥75% of the time over a 6-month period experienced significantly greater A1C reductions and up to 50% decreased incidence of hypoglycemia compared to patients who used their CGM devices <25% of the time (14).

Most studies of stand-alone CGM (i.e., CGM not integrated with an insulin pump) have shown A1C reductions without increased risk of hypoglycemia, but they have not shown *decreases* in hypoglycemia. Hypoglycemia reductions were demonstrated in the ASPIRE study, which compared a SAP device with a more advanced threshold suspend system (Paradigm Veo™ [Medtronic]) that stops insulin delivery when glucose readings fall below a given threshold (usually 70 mg/dL). Threshold suspend significantly reduced the frequency of nocturnal hypoglycemia by 32% (P<.001). Moreover, no severe hypoglycemic events occurred in the threshold suspend group compared with 4 events in the control group (15). Similar results were seen in patients with low baseline A1C and in those whose A1C decreased during the study period (15,16).

A 2012 meta-analysis that included 10 trials comparing real-time CGM to SMBG and 4 studies comparing SAP with MDI+SMBG supported the superiority of CGM over SMBG and SAP devices over MDI+SMBG in terms A1C reduction without increased risk of hypoglycemia (17).

Most RCTs were conducted prior to 2010 and demonstrated benefits despite relatively primitive CGM technology, which contributed to low adherence and high discontinuation rates. Problems with wearability and accuracy have hampered adoption of CGM. Only 6% of the initial enrollment population of the T1D Exchange clinic registry, which began in September 2010, used CGM, and in a 2014 report, 41% of CGM users (9% of T1D Exchange participants at the time of the survey) stopped using their device within a year because of difficulty wearing the device, technical problems, or concerns about data accuracy. The majority of these patients were using older devices (18).

Even with older technology, however, patients are more likely to use CGM more frequently and consistently when they see improvements in glucose trend data, out-of-range glucose levels, and detection of hypoglycemia. Changes that reduce or improve problems with insertion pain, bothersome system alerts, body-fit issues, and other barriers will also improve adherence (19,20). In the DirectNet study (conducted in 2009-2010), children 4 to 10 years of age and their caregivers reported high satisfaction with their devices despite no improvement in A1C or hypoglycemia rates. The DirectNet study also demonstrated the feasibility of CGM for children <4 years of age (21-23).

Technological progress has addressed barriers to CGM, including accuracy, which for many devices now approaches <10% of MARDs, which is considered safe for insulin dosing (4,24). Meanwhile, although CGM usage remains low, it is growing. The number of users in the T1D Exchange clinic registry has more than doubled to 15% in 2016 (1,25,26), and observational data collected in 2014-2015 from the T1D Exchange clinic registry support the benefits of newer devices. In the latest analysis, A1C levels were significantly lower in patients using CGM than those not using CGM, regardless of whether patients administered insulin via a pump (A1C 7.7% versus 8.2%; $P<.001$) or MDI (7.8% versus 8.6%; $P<.001$) (1). No RCTs with newer devices have yet been published, but several are underway.

Professional CGM consists of a real-time or masked (i.e., no data display) CGM that is owned by the clinician and worn by patients for short periods (typically 3 to 5 days; also known as intermittent CGM). The clinician uses the data to provide patient education and/or make changes to treatment regimens to achieve better glycemic control. Several small-scale studies have shown that professional CGM can lead to reductions in A1C, weight loss, and/or reductions in incidence of hypoglycemia in patients with T2D when the clinician uses the data to guide therapeutic changes (27-32). Notably, intermittent real-time CGM use in T2D patients for 12 weeks significantly reduced A1C compared with SMBG, and the difference in A1C was sustained over a 40-week follow-up period. Only about half of the 100 study participants used insulin to control hyperglycemia in this study (32). When used as an educational tool for pregnant women with T1D or T2D, intermittent masked CGM was associated with improved glycemic control in the third trimester, lower birth weight, and a 74% lower risk of macrosomia (33). Masked CGM has also provided valuable insight into the effects of medications in clinical trials and has helped establish normative values for glycemia (34-37).

CGM can be used to identify hypoglycemia in elderly patients and those with hypoglycemia unawareness (30,38,39). Recent studies have pointed to improvements in health-related quality of life (HRQOL), including reduced fear of hypoglycemia (40) and fewer missed school days (41).

Question 1.2. Which patient populations are best served by this technology based on the research?

Consensus conference participants unanimously agreed that real-time CGM should be available to all insulin-using patients regardless of diabetes type, although this conclusion is based entirely on studies conducted in T1D (1,7,9,11,15). Few studies have been conducted in patients with hypoglycemia unawareness due to challenges recruiting a suitable patient population, but it is likely that this population would also benefit from CGM (39). Other patients at risk from hypoglycemia, including the elderly, patients with renal impairment, and athletes should receive next priority (30,38,42). T2D patients who use antihyperglycemic agents other than insulin might also benefit from CGM (32), but the evidence base is inadequate to make a strong recommendation.

Question 1.3. What are the implications for the healthcare system of not addressing glycemic variability that results in short-term acute hypoglycemic episodes/hospitalizations and long-term complications/hyperglycemia?

The most recent estimate of direct medical expenditures for diabetes in the U.S. is $218 billion per year (43); hospitalizations for hypoglycemic and hyperglycemic crises may account for up to $5 billion, based on an estimated cost of approximately $17,500 per hospitalization (44-47). Real-time CGM has the potential to substantially reduce these costs by helping patients prevent hypoglycemia and diabetic ketoacidosis. In the Diabetes Control and Complications Trial, severe hypoglycemia rose exponentially with decreasing A1C (48), whereas no increased or a reduced risk of hypoglycemia occurred with the A1C reductions observed in the JDRF-CGM, STAR3, and ASPIRE studies (5,11,15). A recent modeling study estimated that real-time CGM could reduce annual hospitalizations for hypoglycemia by 32%, which would reduce associated costs by $54 million in a hypothetical population of 46,500 T1D patients (49). Another study conducted in Australia demonstrated an incremental cost-effectiveness ratio (ICER) of $18,257 (AUS dollars) per severe hypoglycemic event avoided (50).

Few studies assessing the cost-effectiveness of CGM have been completed. In a modeling study based on data from the JDRF-CGM, the ICER was $98,679 per quality-adjusted life year (QALY) gained, which is below a recently updated ICER threshold of $109,000/QALY (values below this threshold indicate the therapy is cost-effective) (51,52). In sensitivity analyses, the authors determined that if only 2 glucose monitoring test strips were used per day for device calibration and CGM data were used for insulin dosing, long-term CGM use would produce cost savings compared with standard SMBG (51). Other modeling studies have estimated ICERs ranging from $45,033 to $229,675 (49). Cost-effectiveness studies based on quality of life analyses may not reflect real-world experience,

however, because HRQOL surveys are often insensitive to the effects of CGM. As a result, ICERs may be inflated.

Question 1.4. Is it necessary to review data in different groups to determine the impact on improved control of diabetes, not necessarily only a lower A1C, but a better quality of life?

Although studies conducted to date consistently show the benefits of CGM, additional studies in other populations are needed to substantiate the benefits in those groups (e.g., those with hypoglycemia unawareness). In addition to A1C, studies should assess glycemic variability. HRQOL surveys sensitive to the effects of CGM should be developed and, along with a measure of fear of hypoglycemia, should also be used as endpoints in future studies.

Research Gaps

Prospective RCTs evaluating personal CGM devices in insulin-using patients with T2D are needed to confirm that benefits seen in T1D also apply to this population. Prospective clinical trials are also needed to support CGM benefits as well as determine the suitability of personal versus professional CGM in at-risk groups such as the elderly, pregnant women, patients with kidney disease, patients with hypoglycemia unawareness or otherwise at risk from hypoglycemia, and athletes.

Although modeling studies have highlighted the potential for CGM to reduce healthcare costs, to date, real-world analyses have not demonstrated actual cost reductions by comparing healthcare costs among CGM users versus nonusers. In addition, there is a need for CGM-specific, validated HRQOL surveys, as currently available surveys are insensitive to the effects of CGM.

Question 2. What CGM data are relevant and how should they be reported?

Question 2.1. What information from CGM technology is critical for patients and clinicians to manage diabetes and improve outcomes?

The primary purpose of CGM is to identify glucose patterns, hypoglycemia, and hyperglycemia. Patients using personal CGM should use real-time data to prevent and/or treat hypoglycemia and hyperglycemic excursions, as well as retrospectively to adjust their treatment regimens. On the other hand, clinicians primarily use reports downloaded from personal or professional CGM to make retrospective treatment adjustments. In both cases, the goal is to maximize time in the desired glucose range.

Both patients and clinicians should recognize that blood glucose fluctuations are a dynamic process characterized by the current blood glucose value and the rate and direction of change. Modal day graphs that superimpose multiple days on the same plot are useful for highlighting time of day patterns as well as hypoglycemic and hyperglycemic periods and trends. Meal-related glucose excursions and nighttime glucose patterns should also be assessed. Sensor accuracy is vital and has significantly improved in the past decade. Now most CGM devices have MARD values close to 10% when compared with SMBG or Yellow Springs Instrument glucose values (4,24). No CGM devices are currently approved in the U.S. for insulin dosing or taking action to correct a hypoglycemia event without first confirming the glucose with SMBG. However, most patients use their CGM glucose values for the desired action (insulin dosing or food intake for hypoglycemia) in lieu of SMBG confirmation. Insulin dosing using data from a currently available CGM device is being evaluated (53).

Question 2.2. What key metrics should be considered?

Individual metrics have been discussed in detail elsewhere, including the 2016 AACE/ACE Consensus Statement on Glucose Monitoring (3,54,55). Table 2 summarizes some key metrics discussed by the CGM consensus group, along with their advantages, limitations, and supporting evidence (3,54-62).

Consensus conference participants generally agreed that personal CGM displays should include the following:

- Current glucose value
- Trend arrows showing direction of glucose changes (increases or decreases) and the rate of change for the past few hours
- Glucose values for the past 3, 5, or 7 days at the current time (i.e., modal day)
- Factory-programmed (nonmodifiable) trigger for a hypoglycemic alert set to <70 mg/dL, with optional/programmable alerts at lower values (e.g., <55 mg/dL and <45 mg/dL)
- Factory-programmed (nonmodifiable) hyperglycemic trigger set to >300 mg/dL, with customizable alerts at other hyperglycemic values set by patient and clinician
- Insulin pump data (as applicable), which should be downloadable on the same platform to review insulin dose and glucose excursions simultaneously, such that necessary action can be recommended or taken

Predictive alerts signal CGM users of impending high and low glucose values, whereas rate of change alerts signal when glucose rises or falls at a specified rate. These features may be useful, although the alerts and display information should be clearly distinguishable from the trigger alerts. Users should be able to customize alerts to be discreet (e.g., vibratory or flashing) or audible, but they should be escalating (e.g., with increasing volume or intensity if the user does not respond).

Reports downloaded from personal or professional CGM vary widely in how data are organized and shown (54), and no consensus has yet been reached on optimal

Table 2
Advantages and Limitations of Metrics Recommended for Inclusion in Standardized CGM Reports

Metric	Advantages	Limitations	Supporting evidence and/or detailed discussion
Glucose control measures			
Percent time in glucose range of 70-180 mg/dL[a]	Widely accepted "safe" range of glycemic exposure	May not be appropriate for all patients	Garg and Jovanovic 2006 (56) Bailey et al 2007 (57) Rodbard 2009 (54) Bergenstal et al 2013 (55)
Percent time with glucose >180 mg/dL, >250 mg/dL, >300 mg/dL[a]	Values align with generally accepted levels of extreme hyperglycemia and DKA thresholds	May not be appropriate for all patients	Garg and Jovanovic 2006 (56) Bailey et al 2007 (57) Rodbard 2009 (54) Bergenstal et al 2013 (55)
Percent time with glucose <70 mg/dL, <55 mg/dL, and <45 mg/dL[a]	Values align with generally accepted levels of hypoglycemia and severe hypoglycemia	May not be appropriate for all patients Thresholds at <70, <60, and <50 mg/dL preferred by many clinicians and organizations	Garg and Jovanovic 2006 (56) Bailey et al 2007 (57) Rodbard 2009 (54) Bergenstal et al 2013 (55)
Glycemic variability, reported as SD or %CV	Classic statistical methods generally understood by clinicians; SD of glucose correlates with mean glucose; %CV usually varies systematically depending on glucose level	Reducing glycemic variability not yet proven to independently affect diabetes outcomes in ambulatory patients Values not widely understood by patients SD tends to be higher in patients with higher mean glucose values	Kohnert et al 2009 (58) Rodbard 2009 (54) Bergenstal et al 2013 (55) Bailey et al 2016 (3)
Graphic presentation of glucose values over 1-5 days, including mean at specific times, SD, 95% CI, and mean daily glucose over time, with ability to stratify by weekday, weekend, and day of week	Facilitates detection of consistent patterns in glucose excursions	Graphs may be difficult to interpret due to wide variation in glucose data obtained over several days No agreement among clinicians and industry on optimal modal day presentations	Bailey et al 2016 (3)
Statistics over 7, 15, and 30 days, including mean glucose in the morning, noon, and night; mean daily glucose; percentage of time in range (70-180 mg/dL[a]); number of hypoglycemic episodes; percentage of time in hypoglycemia (<70 mg/dL[a])	Provides information on glycemic trends over time	Potentially difficult and/or time-consuming to report and interpret	Bailey et al 2016 (3)
Calculated (estimated) A1C	Reflects mean glucose and is readily understood by patients and clinicians	Does not reflect hypoglycemic or hyperglycemic values	Rodbard 2009 (54) Bergenstal et al 2013 (55) Bailey et al 2016 (3)
Risk assessment			
LBGI	Weights risk according to more severe hypoglycemic levels	Mathematical formula may need further validation Concept needs to be shown to relate to diabetes outcomes in clinical trials	Kovatchev et al 1998 (59) Rodbard 2009 (54) Fabris et al 2015 (60)
HBGI	Weights risk according to more severe hyperglycemic levels	Mathematical formula may need further validation Concept needs to be shown to relate to diabetes outcomes in clinical trials	Kovatchev et al 1997 (61) Rodbard 2009 (54) Fabris et al 2015 (60)
ADRR (optional)	Combines HBGI and LBGI in one measure	Mathematical formula may need further validation Concept needs to be shown to relate to diabetes outcomes in clinical trials May be more useful/appropriate for SMBG than CGM	Kovatchev et al 2006 (62) Rodbard 2009 (54)

Abbreviations: A1C = glycated hemoglobin; ADRR = average daily risk range; CGM = continuous glucose monitoring; CI = confidence interval; CV = coefficient of variance; DKA = diabetic ketoacidosis; HBGI = high blood glucose index; LBGI = low blood glucose index; SMBG = self-monitoring of blood glucose.
[a] Should include option to customize parameter for individual patients.

graphic displays. The ambulatory glucose profile (AGP), first introduced in 1987 (63) and adapted more recently for CGM (55), or a 24-hour tracing with superimposed insulin, meals, and other markers (64) are useful graphics. A limitation of the AGP and all other modal presentations is that patients do not always keep consistent schedules for meals, snacks, exercise, work, and sleep.

Consensus conference participants agreed that a standardized, "default" report downloadable from all CGM devices should include the parameters described in Table 2 as well as device-related data such as frequency of calibration, frequency of sensor interactions, and point accuracy. Reports should also show the CGM data in context with other variables such as meals, treatments, exercise, illness, insulin boluses, and automated insulin delivery activity. Moreover, systems should permit integration with commonly used step counters, heart rate monitors, and mobile device apps that track meals, exercise, etc., to minimize or avoid manual entry by patients. Innovations such as Bluetooth insulin pens would facilitate passive accumulation of essential insulin dosing data.

Question 2.3. Would standardized reporting support patient management, clinician utilization, and training of clinicians and patients?

Standardized metrics and reporting among available CGM devices would facilitate understanding by patients and clinicians and promote wider adoption of CGM technology. The goal of standardization should be to make CGM reports as universally understandable by clinicians as an electrocardiogram, and reports should also include summary pages geared for patients.

An urgent need is for improved ease of accessing CGM data in terms of both simplicity and speed. Future systems could include automatic uploads to secured data clouds to facilitate remote access by clinicians and caregivers.

Question 2.4. What data are necessary and how should they be standardized?

The default reports from all CGM devices, whether personal or professional (with either masked or real-time displays), should include the metrics listed in Table 2. Manufacturers may differentiate their products by customizing features and data analyses beyond the basic metrics.

Question 2.5. Can unnecessary data distract from key findings? If so, should a series of algorithms be developed to assist with a focused and meaningful analysis and interpretation?

Metrics not listed in Table 2 should be displayed on subsequent pages of CGM reports so they are available to clinicians but do not interfere with review and interpretation of hypoglycemic and hyperglycemic patterns. Pattern-recognition software that identifies high-risk patterns could facilitate interpretation and utilization by clinicians.

Research Gaps

Recommendations for the metrics listed in Table 2 are based primarily on expert opinion of consensus conference participants and others (3,54,55). For example, no clinical studies have examined whether CGM hypoglycemia alerts set at <55 and <45 mg/dL versus <60 and <50 mg/dL would have different effects on patient safety. The risk indices are generally believed to be useful and were shown to predict outcomes in patients with T2D (65), but the impact of changes in the low blood glucose index (LBGI), high blood glucose index (HBGI), and average daily risk range (ADRR) has not been assessed in CGM users.

Question 3. How should the data and reporting be interpreted?

Question 3.1. Are there standard metrics that should inform therapy adjustment?

As discussed under Question 2, a standardized basic report downloadable from all devices would facilitate data interpretation by clinicians and patients. Therapy adjustments should be made on the basis of percent of time within the optimal range (70 to 180 mg/dL for most patients), percent of time above and below this range, and indices of hypoglycemic risk (e.g., LBGI) and glycemic variability (e.g., HBGI and ADRR).

Question 3.2. Should additional patient descriptors based on standardized CGM reporting be included, such as "hypo-unaware," "hyper-unaware," and "high variability"? What are the most important factors clinicians need to focus on when interpreting CGM data?

For patients and clinicians, the identification of nocturnal hypoglycemia, hypoglycemia unawareness, and other hypoglycemia events are of paramount importance in diabetes management, followed by detection of high glycemic variability and hyperglycemia unawareness. CGM reports should not include qualitative descriptors or labels, because these assessments should be left to the clinician as part of the diagnostic process. However, a diagnosis of hypoglycemia unawareness, frequent nocturnal hypoglycemia, or extreme glycemic excursions could be used to justify reimbursement for CGM.

Question 3.3. Who should interpret data to utilize it in an effective way? Who should be authorized to interpret a standardized CGM report that will allow it to be part of permanent medical records and billable service? Is special training or certification necessary? Should the provider interpretation of data be standardized as well?

Patients manage their own diabetes on a day-to-day basis, and their health and safety would benefit from access to CGM data; therefore, whether CGM is used continuously or intermittently, patients should generally be able to see and respond to glucose data and should receive education and

support from their clinicians to ensure acute problems are appropriately addressed. Manufacturers of CGM devices and software are encouraged to provide more patient training courses and materials, especially with online resources.

As described in Question 1.1, CGM without data display (i.e., masked CGM) has demonstrated benefit in T2D when used intermittently in conjunction with advice from clinicians, although more trials of masked CGM with modern devices are needed. In T1D, only near-daily use of personal CGM has been shown to be of benefit (5-9,14,66). Masked CGM is of great value in clinical trials to clarify the action of investigational medications, and CGM results may be used as endpoints in the evaluation of medication efficacy and safety.

Although CGM interpretation has recently become a standard component of endocrinology fellowship training (a practice fully endorsed by AACE/ACE), a large number of clinicians who manage diabetes have not received adequate training in the use and interpretation of CGM, including many practicing endocrinologists, primary care physicians, nurse practitioners, physician assistants, nurses, and certified diabetes educators. CGM training—including the science behind CGM, CGM accuracy, utilization of CGM in clinical practice, interpretation of CGM data, and the delivery of patient education on CGM—should be made widely available to all clinicians involved in diabetes management through relevant medical and diabetes education associations, CGM manufacturers, and continuing medical education providers. Ideally, educational programs and materials would be available through live education as well as print and online materials. However, formal certification in CGM should not be required, as this would result in more barriers and hinder wider adoption of this valuable technology.

AACE/ACE strongly recommends that downloading and interpretation of glucose monitoring data (both SMBG and CGM) should be considered a diabetes management standard of care. As discussed under Question 2, a 1- to 2-page standardized report would facilitate this care process. These reports should be interpreted by trained clinicians but should include summary pages designed to be understood by patients.

Question 3.4. What would be the impact of CGM on patients' frequency of SMBG?

SMBG is currently required for daily calibration of all CGM devices available in the U.S., as well as for insulin dosing, but patient-related errors in SMBG are common (67). CGM innovations have the potential to reduce or eliminate the need for SMBG. A <10% MARD has been suggested as the threshold for CGM accuracy that would permit safe dosing of insulin with CGM, so long as the sensor relays reliable data without signal interruption or loss of sensitivity throughout its lifetime (4). Currently, no CGM devices consistently meet this requirement, and none are yet approved in the U.S. for use in insulin dosing. However, as CGM technology has continued to improve, MARDs have begun to approach the 10% threshold (24), and a factory-calibrated device currently marketed in Europe was shown to have comparable accuracy to SMBG (68). In practice, many patients already use their CGM data without confirmatory SMBG values for insulin dosing. This approach is being assessed in an ongoing trial with a current CGM device (53).

Question 3.5. What outcome measures (behavioral, clinical, laboratory, etc.) can be used by providers and payers to assess the benefits of CGM in their patients and justify decisions on continued need and coverage?

CGM users who lacked full reimbursement were 50% more likely to discontinue CGM in a study involving >10,000 CareLink participants (14), highlighting the need for more studies demonstrating a positive impact on both direct and indirect healthcare spending. Clinical assessments relevant to the benefits of CGM include improvements in glycemic control measures (calculated A1C and glycemic variability metrics) and reductions in the frequency of hypoglycemia, severe hypoglycemia, and number of emergency room visits. Behavioral measurements include changes in the number of days the CGM device was used, frequency of CGM downloads, and frequency of SMBG. In addition, CGM studies could examine endpoints such as improved sleep quality for patients and caregivers; positive changes in absenteeism, workplace disruptions, and work/school performance (e.g., so-called presenteeism, in which individuals' functioning is impaired by diabetes-related events such as hypo- or hyperglycemia); and reduced burden on school resources.

Research and Practice Gaps

Nearly all proposals herein regarding data interpretation are based on expert consensus from the conference rather than clinical studies or other forms of evidence. Research is needed to confirm that CGM devices can be safely used for insulin dosing and to demonstrate the effectiveness and safety of factory-calibrated devices relative to traditional patient-calibrated CGM. Whether approval for insulin dosing and factory calibration would reduce healthcare costs related to SMBG also needs to be studied.

There is a need for pattern recognition software to identify the highest risk patterns, which would facilitate interpretation and utilization of data by clinicians. There was broad consensus at the conference that clinician training programs should be expanded to all healthcare professionals involved in diabetes management. As described in Question 3.5, the impact of CGM on various HRQOL endpoints should be examined to help justify CGM reimbursement.

Question 4. What clinical data are currently available to support expanded CGM coverage by payers as pertains to questions 1 and 3? What additional data are needed?

As described in the preceding sections, a wealth of evidence supports CGM-associated improvements in A1C and reduced risk of hypoglycemia in individuals with T1D, and these benefits are likely for patients with other forms of diabetes using intensive insulin therapy. Furthermore, CGM is likely to provide significant benefits to patients with hypoglycemia unawareness; patients older than 65 years, particularly those at risk from hypoglycemia; women with diabetes who are or are planning to become pregnant and those with gestational diabetes; and patients with kidney disease. Nevertheless, CGM provides benefits only if worn as prescribed and if the data are accessed and used appropriately. Not all patients and/or their caregivers will be willing and able to use the technology, although acceptance and adherence should increase as technological innovations improve wearability, reliability, and accuracy and as economic factors drive down device cost. Additional cost-effectiveness studies are needed to document these changes.

Question 4.1. In view of recent scientific evidence and progress in CGM technology, what are the current gaps in CGM reimbursements and in what priority should reimbursement gaps be addressed?

Two main gaps in reimbursement are the lack of reimbursement for Medicare patients >65 years (pending legislation addresses this gap) and inadequate reimbursement for the time required for clinicians to access and interpret CGM data, as well as provide advice outside of patient visits. In addition, future Current Procedural Technology codes should include personal as well as professional use of CGM to better reflect current practice.

With most currently available CGM technology, data downloads and report printing are time-consuming activities that drain office resources. However, despite the frequency of CGM data downloads being a commonly used and well-accepted quality of care measure, these activities are not currently reimbursed, nor is the time clinicians spend outside of office visits reviewing and analyzing CGM data. All CGM data should be accessible from the electronic medical records, which would improve care and help justify reimbursement.

Question 4.2. What future clinical or technological needs should be addressed to improve outcomes related to CGM?

CGM is a strong research tool, and CGM data should be recognized by governing bodies as a valuable and meaningful endpoint to be used in clinical trials of new drugs and devices for diabetes treatment. The identification of hypoglycemia is as important as the measurement of glycemic reductions in clinical trials.

Efficiency-related improvements would facilitate better patient care as well as reduce care costs. These include advancements in data delivery through cloud-connected or other wireless devices (e.g., Bluetooth) and standardized reports as discussed in prior sections.

CALL FOR ACTION

Patients, clinicians, legislators, patient advocates, insurance companies, regulators, and other interested parties should work together to overcome current barriers to CGM adoption, including those related to reimbursement, patient and clinician training, and ease of use and interpretation. CGM improves glycemic control, reduces hypoglycemia, and may reduce overall costs of diabetes management. Therefore, expanding CGM coverage and use would improve the health of the diabetes population.

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Dr. George Grunberger has served as a consultant and/or speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Novo Nordisk, and Sanofi. He has received research support from AstraZeneca, Eli Lilly, Lexicon, Medtronic, Merck, and Novo Nordisk.

Dr. Henry Anhalt has served as independent director for Tandem Diabetes Care and consultant and/advisor for Abbott Diabetes Care and Eli Lilly.

Dr. Timothy S. Bailey has served as a consultant and/or speaker for Novo Nordisk, Bayer, BD, Medtronic, and Sanofi. He has received research support from Abbott, ACON, Alere, Animas, Bayer, BD, Bristol Myers Squibb, Cebix, Dexcom, GlaxoSmithKline, Halozyme, Insulet, Lifescan, Lilly, Mannkind, Medtronic, Merck, Novo Nordisk, Orexigen, Sanofi, and Tandem.

Dr. Thomas Blevins has served as a speaker for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, and Sanofi. He has received research support from Boehringer Ingelheim, Dexcom, Eli Lilly, Janssen, Lexicon, Medtronic, Merck, Novo Nordisk, and Sanofi.

Dr. Satish K. Garg has received research grants through the University of Colorado from Dexcom,

Medtronic, Abbott, Sanofi, Novo-Nordisk, Eli Lilly, Lexicon, Halozyme, Merck, Mannkind, Dario, Johnson and Johnson, JDRF, NIH and JAEB center/T1D Exchange. He has served as a consultant or advisor for Novo-Nordisk, Eli Lilly, Sanofi, Roche, Lexicon, Merck, and Medtronic.

Dr. Yehuda Handelsman has served as a consultant and/or speaker for Amarin, Amgen, Amylin, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Halozyme, Janssen, Merck, NovoNordisk, Sanofi, and Vivus. He has received research grants from Amgen, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Intarcia, Lexicon, Merck, NovoNordisk, Sanofi, and Takeda.

Dr. Irl B. Hirsch has served as a consultant to Abbott, Becton Dickinson, and Roche. He has received research support from Novo Nordisk.

Dr. Eric A. Orzeck reports he has no relevant financial relationships with any commercial interests.

Dr. Victor Lawrence Roberts has served as a consultant and/or speaker for Novo Nordisk, Advanced Health Media, Boehringer Ingleheim, Decile Ten (Invokana), Medical Exchange International, Medtronic, and Schlessinger & Associates.

Dr. William Tamborlane has served as a consultant for Boehringer Ingelheim, Halozyme, Insuline, Janssen, Medtronic, Novo Nordisk, Sanofi, and UnoMedical.

Amanda M. Justice has received consulting fees from Asahi Kasei and Lexicon.

APPENDIX 1

The Consensus Conference report was based on a 2-day international experts workshop: AACE/ACE Consensus Conference on Continuous Glucose Monitoring

Conference Chair: Vivian A. Fonseca, MD, FACE
Writing Committee: Henry Anhalt, DO, FACE; Timothy Bailey, MD, FACE, FACP, CPI; Thomas Blevins, MD, FACE, FNLA, ECNU; Satish K. Garg, MD; George Grunberger, MD, FACP, FACE; Yehuda Handelsman, MD, FACP, FNLA, FACE; Irl B. Hirsch, MD; Eric A Orzeck, MD, FACP, FACE; Victor Lawrence Roberts, MD, MBA, FACP, FACE; William Tamborlane, MD

The writing committee, AACE, and ACE are grateful to participants for their contribution to the consensus.

Conference Participants:

Medical, Scientific, Professional & Educational Societies

Ashok Balasubramanyam, MD, American Board of Internal Medicine (ABIM); JoJo Dantone, MS, RDN, LDN, CDE, Diabetes Care and Education Group; Guido Freckmann, MD, Institute for Diabetes-Technology GmbH at Ulm University; Barry Ginsberg, MD, PhD, Diabetes Technology Consultants; Lawrence Herman, PA-C, MPA, DFAAPA, American Academy of Physician Assistants; Betty Krauss, Diabetes Care and Education Group; Boris Kovatchev, PhD, University of Virginia School of Medicine; Eric Langer, DO, FACOI, FACE, American College of Osteopathic Internists; David Marrero, PhD, Indiana University Department of Medicine; Robert Ratner, MD, FACE, American Diabetes Association; Cynthia Rice, MPP, JDRF; Laura C. Russell, MA, RD, CDE, Academy of Nutrition and Dietetics; Gary Scheiner, MS, CDE, American Association of Diabetes Educators; Hope Warshaw, MMSc, RD, CDE, BC-ADM, FAADE, American Association of Diabetes Educators; Phyllis Arn Zimmer, MN, FNP, FAANP, FAAN, Nurse Practitioner Healthcare Foundation

Patient/Lay Organizations

Christel Marchand Aprigliano, MS, Diabetes Patient Advocacy Coalition; Amy Bevan, T1D Exchange; Mike Cohen, RPh, MS, ScD, DPS, FASHP, National Patient Safety Foundation & Institute for Safe Medication Practices; Bennet Dunlap, MSHC, Diabetes Patient Advocacy Coalition; Steve Edelman, MD, Taking Control of Your Diabetes; Fred Gallasch, PhD, ACE Foundation Board of Regents Member; Jeff Hitchcock, Children with Diabetes; Mike Hoskins, Diabetes Mine; Stewart Perry, National Diabetes Volunteer Leadership Council; Jennifer Reddan, PharmD, FASHP, National Patient Safety Foundation & Institute for Safe Medication Practices; Jessica Roth, JDRF; Larry Smith, National Diabetes Volunteer Leadership Council

Government/Regulatory, Payers & Large Employers

Pamela Allweiss, MD, MPH, Centers for Disease Control and Prevention; Guillermo Arreaza-Rubin, MD, National Institutes of Health; Stayce Beck, PhD, MPH, U.S. Food and Drug Administration; Helen Burstin, MD, MPH, FACP, National Quality Forum; Sanford Cohen, MD, UnitedHealthcare; Helene D. Clayton-Jeter, OD, U.S. Food and Drug Administration; James Devoll, MD, MPH, Federal Aviation Administration; Teresa de Vries, Healthcare Leadership Council; Judith E. Fradkin, MD, National Institutes of Health

Industry Organizations

Amy Bartee, RN, Eli Lilly and Company/Lilly USA; Harmeet Chhabra, Medtronic Diabetes; Claudia Graham, PhD, DexCom, Inc; Alissa Heizler-Mendoza, MA, RD, CDE, Insulet Corporation; Rolf Hinzmann, MD, PhD, Roche Diabetes Care, Inc; Todd Hobbs, MD, Novo Nordisk, Inc; Laurence B. Katz, PhD, J & J Diabetes Care Companies; Mahmood Kazemi, MD, Abbott Diabetes Care; James Malone, MD, Eli Lilly and Company/Lilly USA; Alan Moses, MD, Novo Nordisk, Inc; David Price, MD, DexCom, Inc; Jimmy Ren, PhD, J & J Diabetes Care Companies; Geoffrey Rezvani, MD, AstraZeneca; James Ruggles, PhD, AstraZeneca; Melissa Schooley, Esq., Medtronic Diabetes; Leo Seman, MD, PhD, Boehringer Ingelheim Pharmaceuticals, Inc; David Simmons, MD, Ascensia Diabetes Care; Paul Strumph, MD, FACE, Lexicon Pharmaceuticals; Andreas Stuhr, MD, MBA, Ascensia Diabetes Care; Bruce Taylor, Roche Diabetes Care, Inc; Susan Thomas, AstraZeneca; Ramakrishna Venugopalan, PhD, MBA, J & J Diabetes Care Companies; Robert Vigersky, MD, Medtronic Diabetes; Howard Zisser, MD, Insulet Corporation

General Session **Agenda, February 20, 2016**	
8:00 AM – 8:10 AM	Welcome & Introductions Dr. George Grunberger, AACE President
8:10 AM – 8:20 AM	AACE Perspective Dr. Vivian Fonseca, Chair, Consensus Conference on Continuous Glucose Monitoring
8:20 AM – 9:05 AM	State-of-the-Art of Glucose Monitoring Technology Dr. Bruce Buckingham
9:05 AM – 9:15 AM	Pillar Breakout Instructions Dr. Vivian Fonseca
9:15 AM – 9:30 AM	Break
Pillar Breakout Sessions	
9:30 AM – 12:00 PM	Medical/Scientific, Professional & Educational Societies *Co-Moderators: Dr. Victor Roberts & Dr. William Tamborlane*
	Patient/Lay Organizations *Co-Moderators: Dr. Irl Hirsch, Dr. Henry Anhalt & Dr. Thomas Blevins*
	Government/Regulatory, Payers & Employers *Co-Moderators: Dr. Eric Orzeck & Dr. Satish Garg*
	Industry Organizations *Co-Moderators: Dr. Timothy Bailey & Dr. Yehuda Handelsman*
12:00 PM – 1:30 PM	Lunch
Pillar Forum	
1:30 PM – 2:15 PM	Question 1: How would patients, clinicians and payers benefit from expanded use of personal and professional CGM?
2:15 PM – 3:00 PM	Question 2: What CGM data are relevant and how should they be reported?
3:00 PM – 3:15 PM	Break
3:15 PM – 4:00 PM	Question 3: How should the data and reporting be interpreted?
4:00 PM – 4:45 PM	Question 4: What clinical data are currently available to support expanded CGM coverage by payers as it pertains to Questions 1 and 3? What additional data are needed?
4:45 PM – 5:00 PM	Conclusion

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From: Brinn, Cindy
To: HCA ST Health Tech Assessment Prog
Subject: Continuous Glucose Monitoring Devices and Molina Coverage
Date: Wednesday, December 6, 2017 5:34:58 PM
Attachments: image003.png
image006.png

Dear Washington State Medicaid Decision Makers,

I have been a diabetes educator for nearly 40 years and the diabetes technology options that have surfaced during the past three years are improving the health of our patients with diabetes. The continuous glucose monitors dramatically reduce the risk of low blood glucose episodes and complications and hospitalizations and improve A1c values by reducing blood glucose elevations. The reduction in high and low blood glucose numbers saves lives and reduces costs significantly in our patients with diabetes.

The magic of continuous glucose monitoring devices (dexcom) and the Medtronic 670G insulin pump with continuous glucose monitor has helped patients know in REAL time when their blood glucose is rising or high or dropping or low. They get ALERTS about what is happening and can respond appropriately with appropriate treatment of the low blood glucose or an insulin injection for a high blood glucose. The finger stick glucose monitoring seems so archaic when compared to these new continuous options. Persons with diabetes requiring insulin need to CONTINUOUSLY know what their blood glucose is to best manage their diabetes and prevent dangerous complications.

I have numerous Molina insured adults that are using very successfully the dexcom sensor and will find it devastating to not have this device available to them any longer. There will certainly be increased low blood glucose episodes and costs for my patients if this device is no longer covered for them. I urge you not move backwards with the management of our patients with diabetes and to CONTINUE the coverage of the dexcom sensor and consider coverage of the 670G insulin pump and sensor. They are absolutely cost effective. Medicare is covering the device!

Thanks for your serious consideration of this cost effective and life changing technology for our Washington Molina patients.

Kind Regards,
Cindy Brinn

Cindy Brinn RD, CDE, BC-ADM | PeaceHealth Medical Group Nutrition & Diabetes Educator
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From: Turk, David
To: HCA ST Health Tech Assessment Prog
Subject: Continuous Glucose Monitoring Devices and Milina Coverage
Date: Thursday, December 7, 2017 7:38:37 AM

Dear Washington State Medicaid Decision Makers,

I am an Endocrinologist in Bellingham, WA. I have been working in this community for the last 23 years. My diabetic practice is quite large. This letter is in response to the recent decision to stop providing continuous glucose monitoring systems (dex com) to adult patients.

The most useful diabetic tool developed in the last 20 years has been the continuous glucose monitor (dex com). This device measures the blood sugar in real time, continuously day and night. It also alerts patients when the blood sugar is high or low and tells the patient whether the glucose level is rising or falling. This device is becoming standard of care – Medicare is now covering its use.

The continuous glucose monitor has revolutionized so many of my patients' lives. They have been able to move from having hypoglycemic episodes, medic calls, emergency room visits, hospitalizations, and sometime even seizures from the low blood sugars to a much more normal life and better diabetic control. If they are not allowed to continue the use of the CGMS, their lives will be devastated. I cannot explain how difficult this will be for these individuals. Considering the cost of medic visits, ER visits for low blood sugars, possible hospitalizations, and complication of diabetes, I cannot believe the CGMS is not a positive with regards to cost.

I ask that you reconsider the decision to not cover CGM systems (dex com) for adults. I believe that decision is a step backward in diabetic care. Thanks you for your consideration.

Sincerely,

David Turk M.D.
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December 7, 2017

Washington State Health Care Authority
Cherry Street Plaza
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Dear members of the HTCC:

On behalf of Dexcom, Inc., I am writing to express my appreciation for selecting continuous glucose monitoring (CGM) for re-review and the opportunity to provide a rebuttal to aspects of the *CGM Update – Draft Evidence Report (November 2017)*. With this letter, I would like to provide some initial general comments followed by more specific remarks.

Although the analysis conducted by the HTCC is quite extensive, I am not confident that the conclusions reached by the committee are relevant to current CGM technology. Because it is generally impractical to study the impact of diabetes treatment on long-term microvascular and macrovascular complications (as such studies must be conducted over many years and require very large samples), change in hemoglobin A1c (HbA1c) is recognized as the standard outcome in diabetes treatment clinical trials due to its strong association with long-term diabetes complications. Additional blood glucose metrics, such as time spent in the target glycemic range and time spent in hypoglycemia, are being increasingly recognized as clinically relevant diabetes treatment outcomes. Therefore, it is important to understand how CGM technology impacts these metrics. Our main current concerns are summarized as follows:

1. Information included in our prior correspondence regarding the Washington HTA has not been incorporated into this analysis.
2. The review applies pharmaceutical evaluation standards to CGM, a rapidly evolving technology, which many be inappropriate and likely underestimates the clinical value of CGM.[1] By basing its conclusions on studies that evaluated now obsolete CGM technology (i.e., devices that have not been commercially available for many years), the HTCC underestimates the clinical benefits of the most current CGM technology.
3. The review fails to recognize the clinical significance of a variety of outcomes from recently completed randomized controlled trials (RCTs) using current-generation CGM and excludes a recent RCT that evaluated the impact of CGM in adults with insulin-treated type 2 diabetes (T2D).

Additionally, the Washington HTA fails to recognize the unique FDA approval and CMS classification of the Dexcom G5 Mobile CGM System as replacement for self-administered blood glucose monitoring (SMBG) in diabetes treatment decisions.

In addition to these major concerns, the HTA assessment fails to recognize the clinical significance of reduction in time spent in hypoglycemia, particularly at night; the demonstration of CGM clinical benefits in patients with both type 1 diabetes (T1D) and T2D; and recently updated professional society recommendations for improved access and benefits of CGM therapy.[2-4] There is evidence that current-generation CGM therapy is cost effective in the short term by reducing the incidence of costly emergency medical treatment of severe hypoglycemia[5] and in the long term by decreasing the risk of microvascular and macrovascular complications.[6]

Therapeutic CGM

The *CGM Update – Draft Evidence Report (November 2017)* includes contradictory statements about the status of FDA-approved CGM devices for replacement of SMBG for therapeutic decision making. Specifically, on page 17, the report incorrectly states that "The FDA has not approved any CGM device for insulin dosing decisions, so persons using CGM must still conduct SMBG several times a day." On page 19, the report correctly states that "The Dexcom G5 Mobile CGM System is the only real-time CGM device approved for therapeutic decision making, as a replacement of traditional finger stick SMBG."

FDA approval of the Dexcom G5 Mobile System as a replacement of SMBG for therapeutic decision making was made in December 2016 based on the recommendations of a full FDA panel hearing.[7] In addition, results from the REPLACE-BG study,[8] a multicenter, randomized, noninferiority clinical trial, confirmed that the use of CGM without confirmatory blood glucose monitoring measurements is as safe and effective as using CGM adjunctive to blood glucose monitoring in well-controlled adults with T1D. In the REPLACE-BG trial, subjects used a Dexcom CGM system running the software currently available in our Dexcom G5 Mobile CGM system. Study results showed that CGM without confirmatory blood glucose monitoring is as safe and effective as using CGM adjunctive to blood glucose monitoring or confirming with a fingerstick and blood glucose meter before making a diabetes treatment decision.[8] Thus, patients using the Dexcom G5 Mobile CGM can reduce their burden of multiple daily finger sticks when using CGM without loss of efficacy or safety.

The demonstrated best-in-class accuracy of the Dexcom G5 Mobile System, coupled with the ability to set real-time hypoglycemic and hyperglycemic alerts, allows it to provide patients and caregivers with a superior method of managing their diabetes care compared to conventional blood glucose monitoring (SMBG).

When discussing the accuracy of CGM, it is helpful to understand the terms involved. Overall accuracy of CGM is measured by the mean absolute relative difference (MARD), which represents the difference between CGM readings and contemporaneous blood glucose values assessed by a laboratory standard. A recent study that evaluated the accuracy of 17 point-of-care SMBG blood glucose meters found that the MARD for the glucose meters ranged from 5.6% to 20.8%, with 9 of the 17 meters having a MARD exceeding 10%.[9] In assessing the safety of insulin dosing based on CGM data, the threshold for accuracy has been recognized at less than 10%.[10] The Dexcom G5 Mobile has an overall MARD of 9.0%.

In 2017, the Centers for Medicare and Medicaid Services (CMS) announced the benefit category of non-adjunctive or "therapeutic" CGM. This provided a categorization for both non-therapeutic and therapeutic CGM, with the latter defined as devices that can be used to replace fingerstick blood glucose testing for diabetes treatment decisions.[11] Such systems are classified as durable medical equipment within the scope of Medicare Part B. Currently, *Dexcom G5 Mobile is the only device which meets the therapeutic CGM device classification*.

On May 18, 2017, a Local Coverage Determination (LCD) for glucose monitoring and Related Policy Article were revised to reflect the CMS ruling.[12] Per the LCD, *therapeutic CGM* may be covered by Medicare when the beneficiary has diabetes and meets all of the following criteria:

- Has been using a blood glucose meter (BGM) and performing frequent (4 or more times a day) testing;
- Is insulin-treated with MDI or a Medicare-covered CSII pump;
- The insulin regimen requires frequent adjustment on the basis of BGM or CGM testing results;
- Within 6 months prior to ordering the CGM, the treating practitioner has an in-person visit with the beneficiary to evaluate their diabetes control and determined that criteria are met; and
- Every 6 months following the initial prescription of CGM, the treating practitioner has an in-person visit with the beneficiary to assess adherence to their CGM and treatment plan.

Use of Meta-Analysis to Evaluate CGM

As mentioned in previous correspondence with the Washington Health Care Authority, experts note that meta-analysis is an inappropriate approach to evaluating rapidly evolving technologies, such as CGM, and may significantly underestimate the efficacy and utility of current CGM systems in diabetes management.[1] CGM is not analogous to a drug which remains the same molecule in all studies. In contrast, CGM technology is constantly evolving, with newer devices having significantly improved accuracy, performance, comfort, and usability compared with older devices (Figure 1). These iterative improvements in technology have resulted in unprecedented high levels of CGM utilization and patient satisfaction.[13-15]

In the recent Diamond and Gold studies,[13-15] patient ratings of satisfaction with CGM and CGM utilization rates were much higher than were previously seen in the JDRF clinical trials completed almost a decade ago.[16,17] Numerous studies have shown that consistent use of CGM is essential for maximum clinical benefit.[18-23] Thus, it is reasonable to conclude that problems associated with early-generation CGM devices may have resulted in poor protocol compliance and distorted the conclusions of such studies as to the magnitude of the potential clinical benefits or lack thereof of CGM.[1]

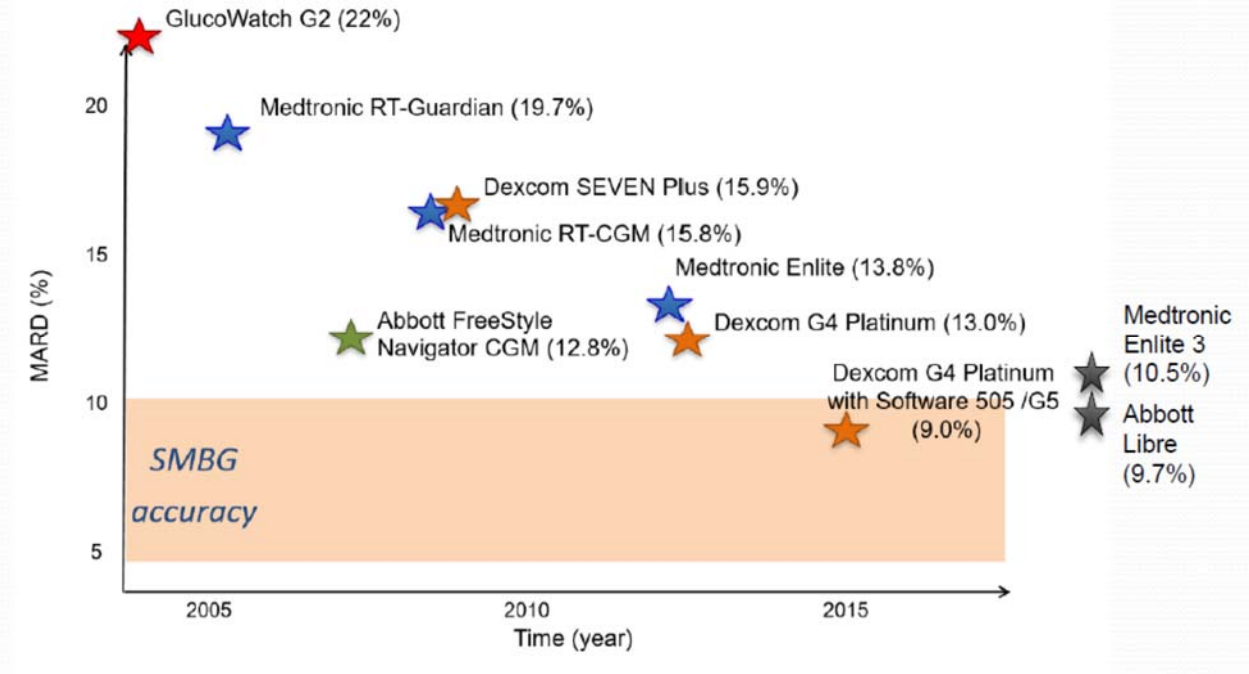

Figure 1: Accuracy of CGM over past 15 years

The vast majority of studies included in the meta-analysis conducted by the HTCC evaluated CGM devices that are now obsolete and no longer commercially available. As shown in Table 1, 19 of the 22 RCTs included in the HTCC meta-analysis that evaluated CGM in children, adolescents, and non-pregnant adults with T1D or T2D utilized CGM technology that is now obsolete and associated with MARD values ranging from 13% to 20%. The accuracy of these previous generations of CGM is significantly less than the accuracy of the Dexcom G5 Mobile System (which has a MARD of 9.0%). By including studies that evaluated older CGM technology in the meta-analysis, the HTCC may have significantly underestimated the potential benefits of this therapeutic category and blunted the impact that patients experience from today's CGM technology.

Table 1: RCTs included in HTCC meta-analysis with obsolete CGM

Study	CGM Device(s) Evaluated	MARD	Obsolete
Deiss, 2006	Guardian REAL-Time Sensor	19.7%	Yes
Hirsch, 2008	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Yoo, 2008	Guardian REAL-Time CGM System	19.7%	Yes
JDRF, 2008	Dexcom Seven Paradigm Real-Time Insulin Pump and CGM System FreeStyle Navigator	17.0% 19.7% 12.8%	Yes
JDRF, 2009	Dexcom Seven Paradigm Real-Time Insulin Pump and CGM System FreeStyle Navigator	17.0% 19.7% 12.8%	Yes
O'Connell, 2009	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Peyrot, 2009	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Raccah, 2009	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Bergenstal, 2010	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Kordonouri, 2010	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Batellino, 2011	FreeStyle Navigator	12.8%	Yes
Ehrhardt, 2011	Dexcom Seven	17.0%	Yes
Hermanides, 2011	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Batellino, 2012	Paradigm REAL-Time Insulin Pump and CGM System	19.7%	Yes
Langeland, 2012	Guardian REAL-Time CGM System	19.7%	Yes
Mauras, 2012	FreeStyle Navigator	12.8%	Yes
Tildesley, 2013	Guardian REAL-Time CGM System	19.7%	Yes
New, 2015	FreeStyle Navigator	12.8%	Yes
Tumminia, 2015	Guardian REAL-Time CGM System	19.7%	Yes
van Beers, 2016	**Medtronic Enlite Sensor**	**10.5%**	**No**
Beck, 2017	**G4 Platinum with 505 software**	**9.0%**	**No**
Lind, 2017	**G4 Platinum with 505 software**	**9.0%**	**No**

Outcomes in HTTC Meta-analysis

Primary HbA1c Outcome

The HbA1c outcome selected as the primary outcome for the HTCC meta-analysis is the proportion of patients achieving an HbA1c level of <7.0% at study end. It is noteworthy that this outcome was not the primary endpoint in any of four RCTs included in the meta-analysis of this outcome. Current American Diabetes Association (ADA) guidelines stress the importance of setting individual patient goals for target HbA1c.[2] The ADA guidelines state that, although a reasonable HbA1c goal for most nonpregnant adults is <7.0%, "more or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations."[2] Thus, defining a "successful" outcome as achieving HbA1c <7.0% is inconsistent with current national diabetes guidelines.

Although the primary endpoint in CGM trials has varied across studies, mean change in HbA1c from baseline is the most commonly specified primary endpoint in RCTs of CGM. A 1% reduction in HbA1c has been associated with both short-term reductions in healthcare utilization and costs and risk of long-term diabetes complications. In a retrospective analysis of administrative data from a large Washington state health maintenance organization, patients with diabetes who achieved a 1% sustained reduction in HbA1c had statistically significant annual cost savings of $685-$950 per patient in the subsequent year.[24] A 1% reduction in HbA1c reduces diabetes-related deaths by 21%, risk of microvascular complications by 37% and myocardial infarction by 14%.[25] We note adults with T1D who received CGM in the Diamond Study reduced their HbA1c by 1% on average.[13]

Time in Nocturnal Hypoglycemia

The HTTC meta-analysis found that, across parallel and crossover trials, CGM appears to be associated with decreased time spent in hypoglycemia at night compared with SMBG. The Committee noted that the clinical significance of this benefit was unclear. In children with diabetes, nocturnal hypoglycemia is very frequent, mostly asymptomatic, and often prolonged (lasting 1-3 hours).[26] Given that an alarm triggered by a CGM low blood glucose reading may be the only way of alerting children and parents of nocturnal hypoglycemia, reducing time spent in nocturnal hypoglycemia is a critical outcome of diabetes management and a clear benefit of CGM.

Hypoglycemia remains the number one barrier to achieving glycemic control and the risk associated with hypoglycemia cannot be understated.[27] The Diamond and Gold trials demonstrated significant impact in the reduction of hypoglycemia through the use of CGM,[28,15] but this benefit was lost when CGM was discontinued.[29] Reduction in the rate of severe hypoglycemia due to CGM is difficult to quantify in RCTs as patients who are at high risk for these events are generally excluded from RCTs and enrolled patients take actions to avoid these events. Designing RCTs adequately powered to detect a statistically significant reduction in the rate of severe hypoglycemia is problematic due to the relative infrequency of severe events and the need for a very large sample size.

However, we feel the following references should be included when assessing impact of CGM on hypoglycemia and other aspects of diabetes clinical care.

Most Recent Clinical Evidence

Randomized Controlled Trials

Adults with T1D

Several recent studies that used current-generation Dexcom CGM systems have added to the already compelling data establishing the benefit of CGM in patients with inadequately-controlled T1D (HbA1c >7.5%). The DIAMOND prospective, randomized, controlled trial (NCT02282397) examined the effects of CGM use in patients (n=158) with HbA1c values ranging from 7.5% to 9.9% in 24 sites across the United States.[13,30] Subjects randomized to CGM demonstrated consistent and sustained use of the technology at 6 months (93% used it 6 or 7 days/week). Use of CGM resulted in a mean HbA1c decrease of 1.0% from baseline at week 24 compared to a 0.4% reduction in the control group. Subjects in the CGM group spent less time in hypoglycemia and experienced significant reductions in diabetes distress and fear of hypoglycemia, and significant improvements in hypoglycemia confidence and well-being, compared with conventionally-monitored patients. Similar benefits were observed across all patient subgroups, including people with lower education levels, lower numeracy skills, higher baseline HbA1c levels, and older ages.

An optional 6-month extension phase offered to people who had used CGM during the index RCT studied the impact of insulin delivery method (MDI versus continuous subcutaneous insulin infusion or CSII) on HbA1c.[28] Results showed that transitioning from MDI to CSII therapy increased time in the target glycemic range, but did not result in a corresponding improvement in HbA1c and increased biochemical hypoglycemia. Subjects in the extension phase continued to use the CGM systems at least 6 days per week.

The GOLD study (NCT02092051) also evaluated the effects of CGM in adults with inadequately-controlled T1D who were being treated with MDI. CGM use was associated with a mean HbA1c level that was 0.43% less than conventional treatment. The GOLD study also demonstrated significant improvements in subjective well-being and treatment satisfaction for subjects using CGM compared with conventional therapy. A separate analysis confirmed that CGM reduced time spent in nocturnal and daytime hypoglycemia and increased confidence in avoiding hypoglycemia and hypoglycemia-related problems. [15,29]

Adults with Insulin-treated T2D

The DIAMOND study included an independently-powered arm that investigated the effects of CGM in patients using MDI therapy to manage their type 2 diabetes (T2D).[14] The results demonstrated that after 24 weeks, participants using CGM lowered their HbA1c levels by an average of 0.8% from baseline. Compared to the control group, the CGM group also spent less time in hyperglycemia and more time spent in the target range. The CGM group increased time in range by 1.3 hours compared to baseline, and 0.6 hours compared to the control group. The HbA1c reductions did not depend on age, educational attainment, or numeracy skills, and adherence to CGM therapy was remarkably high, with 93% of participants using CGM 6 or 7 days per week at the end of the study. Participants also reported a high level of satisfaction and a relatively low level of perceived hassles. *The results of this study were not included in the HTCC CGM Update*.

Children and Adolescents with T1D

The T1D Exchange Clinic Registry follows over 26,000 patients with T1D, almost 15,000 of whom are younger than 18. Recent Registry publications have confirmed that CGM use is increasing rapidly, especially among very young children. The mean HbA1c values among CGM users and non-users in the Registry were recently reported as 8.1% and 8.9%, respectively.[31] CGM use in every age cohort examined was associated with lower HbA1c values, as shown in Figure 2.[32] Separate data from two sensor accuracy studies in youth ages 2-17 years[33] showed that use of CGM had the potential to increase glucose time in range and improve glycemic outcomes.

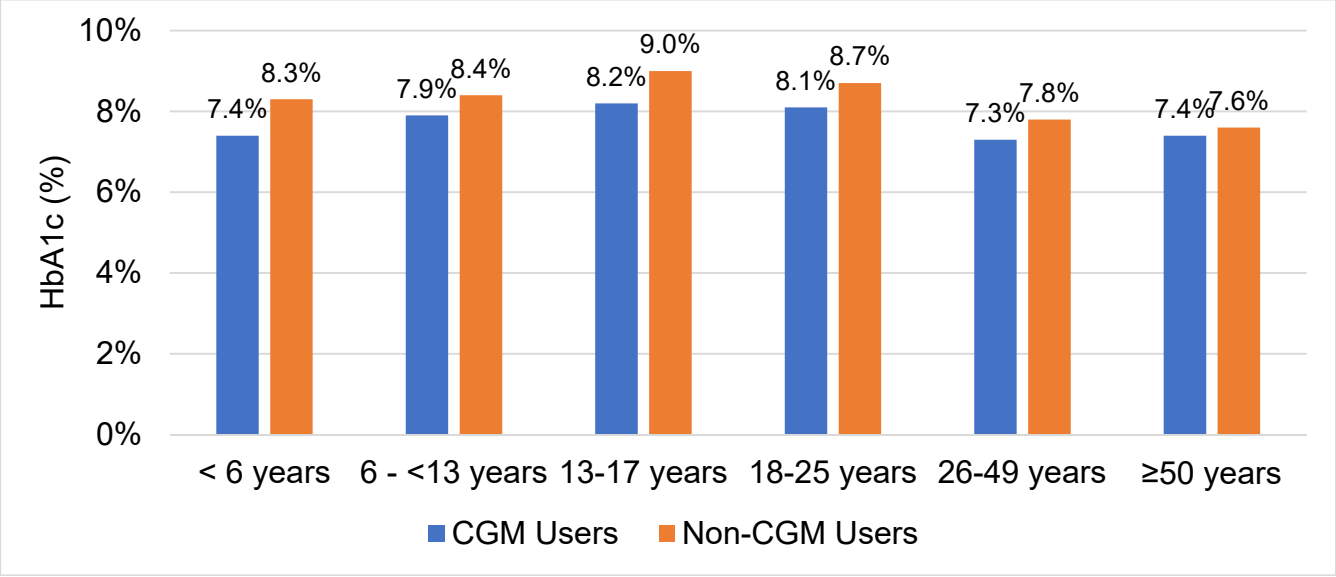

Figure 2: HbA1c values for CGM users vs non-CGM users in the T1D Exchange Registry

Real-World Studies

Data from two recently published real-world studies show that CGM used in conjunction with MDI is as effective as the combination of CGM and CSII therapy for improving glycemic control. The COMISAIR study was a nonrandomized, prospective, real-life clinical trial in which T1D patients received MDI or CSII therapy in combination with either CGM or SMBG.[34] Both insulin delivery modalities combined with CGM provided significant and comparable decreases in HbA1c with concurrent reduction in time spent in hypoglycemia compared to insulin therapy with conventional blood glucose monitoring after 1 year. The COMISAIR study followed some patients for up to 2 years, and the recently-reported results from this long-term study confirmed the durability of the HbA1c benefit for users of CGM, regardless of insulin delivery method.[34]

An analysis of data from the T1D Exchange registry examined the impact of CGM on HbA1c in 17,731 T1D patients treated with MDI or CSII.[35] Among CGM users, mean HbA1c was similar in the MDI and CSII groups (7.6% vs. 7.7%, P=0.82); however, HbA1c in both CGM groups was lower than among patients using CSII + SMBG (8.3%, P<0.0001) and MDI + SMBG (8.8%, P<0.0001). Results were similar in adults and youth (Figure 3).

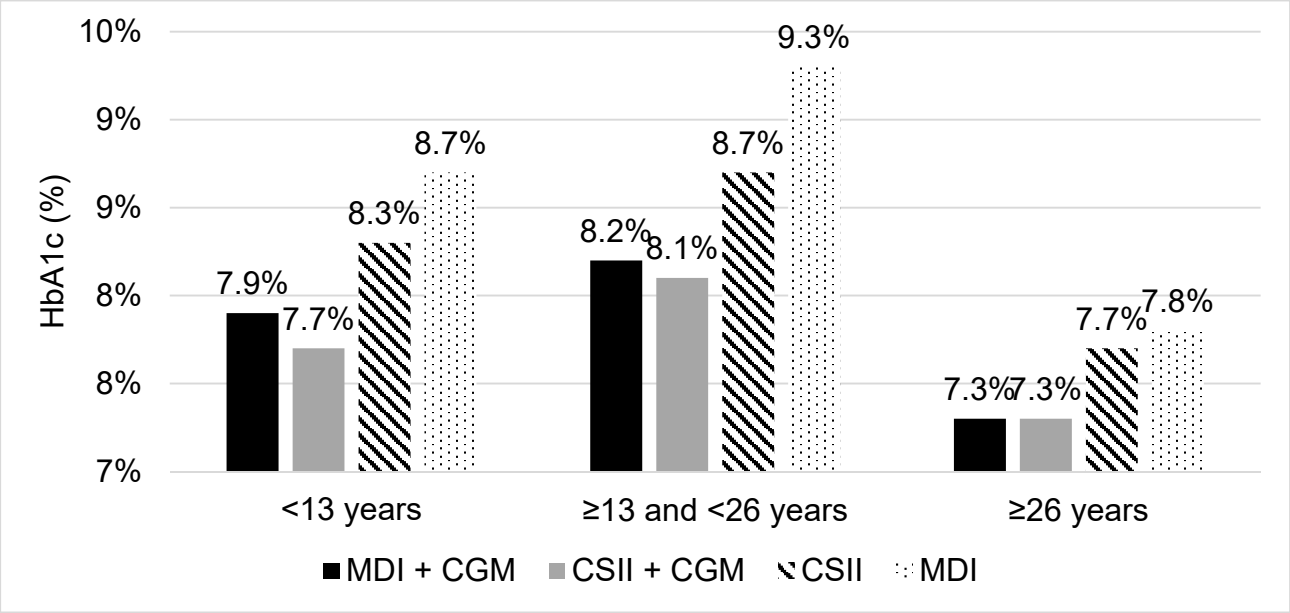

Figure 3: Mean HbA1c according to insulin modality/CGM use status. Solid black bar, MDI + CGM; solid gray bar, CSII + CGM; black and white striped bar, CSII only; black dotted bar, MDI only.

Professional Society Recommendations

The rapid adoption and proven benefits of CGM have prompted several professional societies to issue position statements or consensus recommendations regarding its use in of several professional societies. The American Diabetes Association recognizes that success with CGM depends in part on consistent use and asserts that CGM, in conjunction with intensive insulin therapy, is a useful tool to lower HbA1c in adults (ages

≥25 years) with T1D and can be helpful in lowering HbA1c in children, teens and younger adults.[2]

A consensus statement from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology states that CGM should be available to all insulin-using patients regardless of diabetes type.[36] The AACE outpatient glucose monitoring consensus statement recommends personal CGM for patients with T1D diabetes and with history of severe hypoglycemia or hypoglycemia unawareness, and to assist in the correction of hyperglycemia in patients not at goal. [3]

The Endocrine Society recommends CGM for adult patients with T1D whose HbA1c is above 7% who are able to wear the devices on a daily basis, or in patients who experience significant hypoglycemia.[4] The Association of Children's Diabetes Clinicians, which published a clinical guideline for use of CGM in children diabetes in 2017, emphasized that CGM *with alarms* can be considered for all children on MDI or CSII therapy (Grade A), and should be considered for children of any age with a history of hypoglycemic seizure (Grade B).[37]

Economic Value of CGM

Although HTCC review considered a number of cost-utility analyses that evaluate the long-term cost-effectiveness of CGM, the review omitted a recently published study that estimated the short-term cost implications of providing CGM to insulin-treated diabetes patients at high risk for costly emergency treatment of severe hypoglycemia.[5] This analysis found that providing CGM to all patients with insulin-treated diabetes who are at high risk for severe hypoglycemia due to hypoglycemia unawareness would result in a 1-year cost savings of $946 to $1346 per patient. This savings is a conservative estimate because it does not account for potential cost savings accrued by reducing the incidence of long-term microvascular and macrovascular complications by lowering HbA1c. Although the ability of CGM to reduce the incidence of severe hypoglycemic has not been well studied, a randomized controlled crossover study by van Beers et al. found that patients with T1D and hypoglycemia unawareness had 59% fewer severe hypoglycemia episodes when using CGM than when using SMBG.[38]

In conclusion, therapeutic CGM is a significant advancement in CGM technology with superior accuracy and demonstrated clinical benefits. We feel the current HTA does not adequately recognize therapeutic CGM as a distinct class of device with unique benefits and has based much of its conclusions on technology that is discontinued and not reflective of current device performance. In contrast, regulatory agencies and payers have recognized that advances in CGM technology provide important benefits to patients and that CGM should be more broadly covered (e.g., therapeutic CGM is now a CMS covered benefit). We urge the technology research team to examine the most current evidence, clinical expertise, and Medicare criteria and Medicaid policies when evaluating the strength of evidence for CGM.

Respectfully,

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New York Department of Health
Evidence-based Review Process
for Coverage Determinations

Medtronic Dossier Submission
Continuous Glucose Monitoring Systems for Diabetes

August 2017

Table of Contents

Submission Checklist

The following information should be included in the dossier submission:

- ✓ **Overview, Contact Information, PICO and Executive Summary**
- ✓ **Service Rationale**
- ✓ **References & Quality Appraisal Ratings**
    - **Full PDF copies of all references and articles cited**
    - **Completed Quality Appraisal Checklist for each study submitted**
- ✓ **Overall Strength of Body of Evidence**
- ✓ **Net Impact Worksheet**
- ✓ **Supporting Documents (e.g., FDA approval letter, IRB protocol, trial registration –*if applicable*)**

All forms should be completed in 12 pt Calibri font with one-inch margins. **Please do not exceed 6,000 words on the Service Rationale** (excluding PDF copies of references). Failure to follow these submission requirements will result in the entire dossier submission not being reviewed. Please submit six hard copies and four electronic copies (USB devices) of your dossier submission to:

New York State Department of Health
Office of Health Insurance Programs
Empire State Plaza
Corning Tower (OCP-720)
Albany, NY 12237
ATTN: Dossier Review Unit

Overview and Contact Information

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Technology Information

Service Under Review	Continuous Glucose Monitoring (CGM)
Manufacturer(s)	*The following manufacturers provide Personal and Professional CGM:* Medtronic Diabetes | Northridge California Dexcom | San Diego, California *The following manufacturer provides Professional CGM:* Abbott | Abbott Park, Illinois
Description of Service	***Continuous Glucose Monitoring (long term/personal):*** Personal CGM monitors patients' glucose levels and provides regular updates of these readings. Personal CGM systems provide up to 288 glucose readings per day allowing patients and their physicians to evaluate the changes in interstitial glucose levels. The assessment of the daily glycemic variability empowers the patient to identify causes of hyper- and hypoglycemic events in collaboration with the care team and to adapt their therapy plan accordingly. Medtronic's CGM connects to Medtronic's insulin pump (covered by NY Medicaid) which then automatically takes action based on the sensor glucose readings. With this connected CGM, Medtronic's pump (already covered by NY Medicaid) can sense, interpret and respond to the trends in glucose values because of the CGM. With stand-alone CGM, the user has to take action and manually adjust their therapy. ***Continuous Glucose Monitoring (short term/professional):*** Professional CGM is a Holter-type device, measuring glucose subcutaneously in the interstitial fluid and allowing for up to 6 days of records blinded to patients. It is meant to be primarily used by the health care professional to adjust treatment appropriately through the retrospective analysis of recorded data. Potential indications for the use of professional CGM

Applicable Codes	
What HCPCS or CPT® codes can be used to bill for this service? ***Please list all applicable codes.***	***Continuous Glucose Monitoring (long term/personal):*** Personal CGM reimbursement is subject to benefit design and has dual coverage under both DME Medical and Pharmacy. Medtronic Diabetes uses the following HCPCS codes when billing through DME: **A9276** Sensor; invasive (e.g., subcutaneous), disposable, for use with interstitial continuous glucose monitoring system **A9277** Transmitter; external, for use with interstitial continuous glucose monitoring system **A9278** Receiver (monitor); external, for use with interstitial continuous glucose monitoring system ***Continuous Glucose Monitoring (short term/professional):*** CPT Codes **95250** Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording. **95251** Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; interpretation and report.

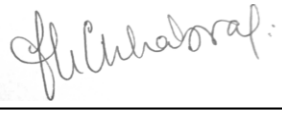
PICO

The Population, Intervention, Comparator, and Outcome framework, otherwise known as the PICO, helps to define the literature search parameters and forms the basis of establishing specific research questions on a topic. For services with wide applicability, the PICO can assist in focusing the evidence review to a manageable research topic. An example topic submission is available in Appendix A.

Table 1: PICO Criteria

Population(s)	Type 1 & Type 2 Diabetes (all age groups); Gestational Diabetes
Intervention(s)	Continuous glucose monitoring (CGM) systems; includes real and retrospective CGM; +/- self monitor blood glucose (SMBG); CGM + insulin pump therapy (Continuous subcutaneous insulin infusion CSII); sensor augmented pumps (ON only)
Comparator(s)	Self-monitor blood glucose levels (SMBG i.e. finger sticks, with any combination of insulin delivery systems – CSII or MDI); also can include Sensor Augmented Pumps (with CGM/sensor/low glucose suspend in OFF); other CGM devices
Outcomes (please list up to five outcomes to be considered in this review)	Outcome (e.g., cardiac events)
	1. Change in glycosylated hemoglobin (HbA1c)
	2. Hyperglycemia events
	3. Hypoglycemia events
	4. Ketoacidotic events
	5. Health Related Quality of life
Harms (please list all patient important harms associated with this product, provide a timeframe for each harm, and list in order of severity and patient importance (e.g., mortality should be listed first if applicable)	1. Local adverse effects: (skin irritation, wound infection Sensor site occlusion)
	2. Serious Adverse Events
	3. Pain
	4. Mortality (any cause)

Please affirm that the dossier submission is complete and accurate and includes all available relevant data.



Signature of Dossier Submitter

August 25th, 2017

Date

Executive Summary

Please provide an overview of the service in the space provided below (250 to 750 words). The summary should include a short description of the service, included evidence, and all related harms. The executive summary may be used on the Department's website and should be written at a reading level for general public consumption.

Blood glucose monitoring is an essential part of diabetes management and is used to optimize glycemic control. Good control of blood glucose levels plays an important role in reducing the risk of serious long-term complications, including microvascular damage (nephropathy, retinopathy) as well as macrovascular damage (cardiovascular disease).[1,2] Regular testing of blood glucose levels is therefore recommended. This allows patients with diabetes to adjust therapy (insulin dosage) appropriately.

Continuous glucose monitoring (CGM) is a way to measure glucose levels in real-time throughout the day and night. A tiny electrode called a glucose sensor is inserted under the skin to measure glucose levels in tissue fluid. It is connected to a transmitter that sends the information via wireless radio frequency to a monitoring and display device. The device can detect and notify patients if their glucose is reaching a high or low limit.

Unlike stand-alone CGM, Medtronic's CGM connects to a Medtronic insulin pump (covered by New York Medicaid). The Medtronic MiniMed 530G System (pump plus CGM, also known as a *sensor augmented pump* or SAP) will automatically suspend the delivery of insulin when the CGM reading reaches a low sensor value, thus preventing a hypoglycemic event. Additionally, the Medtronic MiniMed 670G SAP System senses, interprets and automatically responds to trends in the glucose levels based on the CGM reading. The 670G System will automatically suspend the delivery of insulin when the CGM readings predict the sensor values are dropping rapidly, thus preventing a hypoglycemic event, and will also automatically increase the basal insulin if the sensor values are rapidly rising, avoiding a hyperglycemic event or diabetic ketoacidosis (DKA). The integrated Medtronic CGM and Insulin Pump, in which the pump senses, interprets and responds to trends, is an example of the progress Medtronic has made towards an autonomous artificial pancreas system for individuals with diabetes.

In order to assess the effectiveness and safety of CGM therapies in the management of diabetes (T1DM, T2DM and GDM) a comprehensive literature search was performed. Eight Health Technology Assessments (HTAs)[3–14], 12 Systematic reviews (SRs)[15–26] and 17 Randomized Controlled Trials (RCTs)[27–42,43] were included for review.

Overall, the HTA/SR evidence suggested that real time-CGM (rt-CGM), including SAP therapies is superior to self-monitoring of blood glucose (SMBG) and other treatments in lowering HbA1c, without increasing or decreasing the risk of severe hypoglycemia in T1DM. RCTs that examined

Medtronic-specific CGM and SAP use in diabetes patients showed significant benefits in T1DM patients. The **STAR-3 study**[36] was a 1-year, multicenter, RCT that enrolled 485 adults and children with uncontrolled T1DM (HbA1c level between 7.4% and 9.5%) despite MDI therapy. Patients were randomized to a SAP with the Medtronic MiniMed Paradigm REAL-Time™ system or to multiple daily injections (MDI) and SBGM. At baseline, the mean HbA1c, for children and adults, was 8.3% in both study groups. Adult patients experienced HbA1c reduction, showing an improvement in overall glucose control. CGM has been shown to be safe in many clinical studies. Adverse events are usually minor in nature and often localized to skin irritations around the sensor needle (see **Table 11**).

Published economic evaluations have shown that rt-CGM has the potential to substantially reduce healthcare costs by helping patients prevent hypoglycemia and diabetic ketoacidosis.[44–46] A recent US modeling study estimated that rt-CGM could reduce annual hospitalizations for hypoglycemia by 32%, which would reduce associated costs by $54 million in a hypothetical population of 46,500 T1D patients.[44] In addition, for the three years ending in 2013, according to federal government data, approximately 1.6 million adult New Yorkers a year had been diagnosed with diabetes.[47] The cost of treating these patients is high. The Department of Health reports the overall annual cost of diabetes in New York, attributable to both direct medical costs and lost productivity, is $12 billion for all payers, including Medicaid. [47]

In 2016, the *American Association of Clinical Endocrinologists* and *the American College of Endocrinology* (AACE/ACE) released a Consensus Statement on CGM use in the USA.[48] They concluded that **"*CGM improves glycemic control, reduces hypoglycemia, and may reduce overall costs of diabetes management. Expanding CGM coverage and utilization is likely to improve the health outcomes of people with diabetes*".**

Service Rationale

The following questions inquire about the safety and efficacy of the service under review and its applicability to the New York Medicaid population. The use of the term "service" refers to medical or surgical treatment procedures, devices, and diagnostics. Please cite your responses and list all references in the *References & Quality Appraisal Ratings* section. Please answer the questions below using 12 pt Calibri font with one inch margins. DO NOT EXCEED 6,000 WORDS TOTAL IN ANSWERING THE QUESTIONS BELOW.

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1. The service must have final approval from the appropriate US governmental regulatory bodies (e.g., FDA), if applicable.

a) What is/are the licensed use(s) of this service?

MiniMed™ 670G System *(Source: MP6025992-015DOC)*

The Medtronic MiniMed 670G system is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of Type 1 diabetes mellitus in persons, fourteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 670G System includes SmartGuard™ technology, which can be programmed to automatically adjust delivery of basal insulin based on Continuous Glucose Monitor sensor glucose values, and can suspend delivery of insulin when the sensor glucose value falls below or is predicted to fall below predefined threshold values

The Medtronic MiniMed 670G System consists of the following devices: MiniMed 670G Insulin Pump, the Guardian™ Link (3) Transmitter, the Guardian™ Sensor (3), One-press Serter™, and the CONTOUR NEXT™ Link 2.4 Glucose Meter. The system requires a prescription.

The Guardian Sensor (3) is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on values provided by the Guardian Sensor (3).

WARNING: Medtronic performed an evaluation of the MiniMed 670G system and determined that it may not be safe for use in children under the age of 7 because of the way that the system is designed and the daily insulin requirements. Therefore this device should not be used in anyone under the age of 7 years old. This device should also not be used in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

WARNING: Do not use the Suspend on low feature to prevent or treat low glucose. Always confirm your sensor glucose reading using your BG meter, and follow the instructions of

your healthcare professional to treat low glucose. Using Suspend on low alone to prevent or treat low glucose may result in prolonged hypoglycemia.

MiniMed™ 630G System with SmartGuard *(Source:MP6026157-011DOC)*

The MiniMed 630G System with SmartGuard is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of diabetes mellitus in persons, sixteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 630G System includes SmartGuard which can be programmed to temporarily suspend delivery of insulin for up to two hours when the sensor glucose value falls below a predefined threshold value.

The MiniMed 630G System with SmartGuard consists of the following devices: MiniMed 630G Insulin Pump, Enlite™ Sensor, One-Press serter, Guardian™ Link Transmitter System, Carelink™ USB, Bayer's CONTOUR NEXT™ LINK 2.4 Wireless Meter, and Bayer's CONTOUR NEXT Test StripsThe system requires a prescription.

The MiniMed 630G System with SmartGuard is not intended to be used directly for making therapy adjusments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on values proided by the MiniMed 630G System.

The MiniMed 630G System with SmartGuard is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the SmartGuard Suspend on low alarm to take measures to prevent or treat hypoglycemia themselves. Therapy to prevent or treat hypoglycemia should be administered according to the recommendations of the user's healthcare provider.

MiniMed™ 530G System *(Source: MP6025813-012DOC)*

The MiniMed 530G System is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of diabetes mellitus in persons, sixteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 530G System can be programmed to automatically suspend delivery of insulin for up to two hours when the sensor glucose value falls below a predefined threshold value.

The MiniMed 530G System consists of the following devices tht can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite Sensor, Enlite™ Serter, the MiniLink™ Real-Time System, Bayer's CONTOUR NEXT LINK Wireless Meter, CareLink™ Pro Therapy Management Software for Diabetes, and CareLink™ Personal Therapy Management Software for Diabetes. The system requires a prescription.

The MiniMed 530G System is not intended to be used directly for making therapy adjusments,

but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on values provided by the MiniMed 530G System.

The MiniMed 530G System is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the Threshold Suspend alarm to take measures to prevent or treat hypoglycemia themselves. Therapy to prevent or treat hypoglycemia should be administered according to the recommendations of the user's healthcare provider.

iPro™2 ***(Source: MP6025651-012DOC)***

The iPro2 Recorder is to be used with either Enlite sensor or Sof™-sensor and is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace, blood glucose information obtained using standard home glucose monitoring devices. The information collected by the iPro2 digital recorder may be uploaded to a computer (with Internet access) and reviewed by healthcare professionals. The information may allow identification of patterns of glucose-level excursions above and below a desired range, facilitating therapy adjustments, which may minimize these excursions.

This iPro2 system:

• is intended for prescription use only.

• does not allow data to be made available directly to patients in real time.

• provides data that will be available for review by physicians after the recording interval (up to 144 hours).

•is intended for occasional rather than everyday use.

• is to be used only as a supplement to, and not a replacement for, standard invasive measurement.

b) Does the service have FDA or other regulatory agency approval and for what use(s)?

Product	FDA Approval
MiniMed 530G	**P120010**
MiniMed 630G	**P150001**
MiniMed 670G	**P160017**
iPro 2	**P150029**

c) **What approval process was employed (e.g., 510(k), Premarket Approval, Investigational Device Exemption)?**

Premarket Approvals.

d) **Please submit approval letter from the FDA or other regulatory agency, if applicable**.

See **Appendix H**

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

a) **Please specify how the submitted references demonstrate the efficacy and/or effectiveness of this service.**

Efficacy/Effectiveness:

A comprehensive search on the use of the Continuous Glucose Monitoring (CGM) in the management of diabetes (T1DM, T2DM and GDM) was performed in March 2017 (see **Appendix E**). Over 1500 citations published from 2005 onwards were retrieved for review. **Given the large evidence base for CGM it was deemed necessary to include only the highest level of evidence for review in this submission**. Hence the submission will focus on published Health Technology Assessment (HTA) reports, systematic reviews (SR's) and randomized controlled trials (RCTs) that compare Medtronic CGM technologies with self-monitored blood glucose (SMBG) regimens and/or other glucose monitoring technologies.

HEALTH TECHNOLOGY ASSESSMENTS (HTAS)

Eight HTAs[3–14] on CGM technologies from 7 different countries published from 2010 to 2016 were reviewed. The main characteristics of the 8 HTAs are summarized in **Table 15.** The HTA reports included for review were all of *good* quality and included only RCTs as their main source of evidence for CGM.

The most recent HTA reports and those conducted from a US perspective are discussed in more detail below:

ECRI Institute 2016[3]

In July 2016 the ECRI Institute in the USA published an emerging technology report on threshold-suspend/Low-glucose-suspend insulin delivery systems for managing hypoglycemia in patients with T1DM.[3] While the report focused on the Medtronic MiniMed 530G with Enlite insulin delivery system, the evidence review included any Sensor Augmented Pump (SAP) with threshold suspend or LGS insulin delivery. ECRI concluded that compared with SAP therapy alone, SAP therapy with threshold-suspend/LGS resulted in fewer nocturnal hypoglycemic

episodes requiring assistance for treatment or resulting in seizure or coma. (*Strength of evidence: Moderate*).

NICE 2016[4,49]

In 2016, the United Kingdom's *National Institute for Health and Care Excellence* (NICE) issued positive guidance for the use of Medtronic insulin pump systems integrated with CGM, for managing Type 1 diabetes and the avoidance of potentially life-threatening hypoglycemic episodes.[49] The positive guidance was based on an extensive systematic literature review and economic evaluation of SAP therapy that is available in the UK.[4] The overall objective of this review was to summarize the evidence on the clinical effectiveness and cost-effectiveness of the MiniMed™ Paradigm Veo system and the Vibe™ (Animas Corporation, West Chester, PA, USA) and G4 PLATINUM™ CGM system (Dexcom Inc., San Diego, CA, USA) for the management of T1DM in adults and children.

What did they include? 19 studies examining clinical effectiveness were included in the review. The study populations eligible for inclusion in this HTA were adults, including pregnant women, and children with T1DM, and the relevant setting was self-use supervised by primary or secondary care. The interventions were sensor augment pumps (SAP) namely Medtronic Veo system and the Vibe™ described above and the main outcomes were glycated hemoglobin (HbA1c) levels, the frequency of hyperglycemic events and the frequency of hypoglycemic events.[4]

Twelve studies were included in the analyses for adults. The main conclusion from these trials was that the MiniMed Paradigm Veo system reduces hypoglycemic events in adults more than the integrated CSII + CGM system without any differences in other outcomes, including changes in HbA1c levels. Nocturnal hypoglycemic events occurred 31.8% less frequently in the MiniMed Veo group than in the integrated Continuous Subcutaneous Insulin Infusion (CSII) + CGM group {1.5 events per patient per week [standard deviation (SD) 1.0 event per patient per week] vs. 2.2 events per patient per week (SD 1.3 events per patient per week); $p < 0.001$}.[4]

Similarly, the MiniMed Veo group had significantly lower rates of combined daytime and night-time events than the integrated CSII + CGM group [3.3 events per patient per week (SD 2.0 events per patient per week) vs. 4.7 events per patient per week (SD 2.7 events per patient per week); $p < 0.001$]. Indirect evidence suggested that that there are no significant differences between the MiniMed Paradigm Veo system, CSII + SMBG and MDI + SMBG with regard to change in HbA1c levels at 3-month follow-up. However, if all studies are combined (i.e. combining different follow-up times and including mixed populations), the MiniMed Paradigm Veo system was significantly better than MDI + SMBG, with regard to HbA1c levels [weighted mean difference (WMD) –0.66%; 95% confidence interval (CI) –1.05% to –0.27%].[4]

What did NICE conclude? Overall, the evidence suggests that the MiniMed Paradigm Veo system reduces hypoglycemic events more than other treatments, without any differences in other outcomes, including changes in HbA1c levels. In addition, they found significant results in favor of the integrated CSII + CGM system over MDI + SMBG with regard to HbA1c levels and quality of life.[4]

IQWIG 2015[5]

In 2015, the German *Institute for Quality and Efficiency in Health Care* (IQWIG) published the results of their assessment on real time (rt)-CGM measurement devices in diabetes mellitus patients treated with insulin regarding patient-relevant outcomes. From their meta-analysis of published RCTs their conclusions in regards to effectiveness of rt-CGM (+SMBG) in comparison with SMBG alone, was;

- Proof of benefit in adults (> 18 years) regarding the joint consideration of severe hypoglycemia and HbA1c value (the joint consideration was based on a hint of superiority regarding severe hypoglycemia and proof of superiority regarding HbA1c value)
- An indication of benefit in children (< 18 years) regarding the joint consideration of severe hypoglycemia and HbA1c value (the joint consideration was based on a hint of superiority regarding severe hypoglycemia and an indication of superiority regarding HbA1c value)
- An indication of benefit in adults (> 18 years) regarding the joint consideration of serious hypoglycemia and HbA1c value (the joint consideration was based on the fact that, regarding serious hypoglycemia, there was no hint of superiority and an uncertainty of the available data as well as proof of superiority regarding HbA1c value)

AHRQ 2012[12,13,50] *(& update in 2016)*[11]

In 2012 the *Agency for Health Research and Quality* (AHRQ) in the US published their HTA on the use of rt-CGM in IDDM patients.[12,13] The HTA report focused on two key research questions, while the first question examined the evidence for insulin pump therapy versus multiple daily injections (MDI), the second half of the review analyzed CGM use with the following research question:

Key Question 2. *In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (real time continuous glucose monitoring [rt-CGM] vs. self-monitoring of blood glucose [SMBG]) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy)?*

What the AHRQ found in regards to CGM efficacy and effectiveness:
Eight RCTs of rt-CGM vs SMBG were included as the primary source of evidence for this review. Compared with the SMBG group, the rt-CGM group achieved -0.3% (95% CI, -0.37 to -0.22; P < 0.001) lower HbA1c. A sensitivity analysis showed this effect to be greater in studies where sensor compliance was 60% or greater (-0.36%, 95% CI, -0.44 to -0.27; P = 0.119). In addition, rt-CGM was associated with lower HbA1c compared with SMBG in individuals 18 years of age or younger.

The intervention groups did not differ in the rate of severe hypoglycemia; however, there was a significant reduction in the time spent in the hyperglycemic range. A few included RCTs that evaluated QOL found no difference in general and diabetes-specific QOL between the two intervention groups. Interestingly the results from this meta-analysis were similar to previous systematic reviews where rt-CGM was found to lower HbA1c more than SMBG (e.g. -0.28% in the AHRQ analysis vs. -0.30% in Pickup et al.2011[22]) and that there was no difference in severe hypoglycemia in the two intervention groups.

SAP use resulted in a statistically and clinically significantly greater reduction of -0.61% in HbA1c compared with MDI/SMBG use in non-pregnant individuals with type 1 diabetes. The evidence was insufficient to draw definitive conclusions about severe hypoglycemia or QOL.

The findings from the AHRQ 2012 HTA report also indicate that rt-CGM is superior to SMBG in lowering HbA1c, without increasing or decreasing the risk of severe hypoglycemia, in non-pregnant individuals with T1DM, particularly those who are compliant with wearing the monitoring device. **The investigators also found the addition of rt-CGM to CSII was superior to MDI/SMBG in lowering HBA1c.** Thus, the addition of this monitoring method to SMBG and intensive insulin therapy can assist in achieving glycemic targets in individuals with type 1 diabetes.

In February 2016 the AHRQ published an updated review of the rt-CGM evidence as part of their Systematic Review Surveillance Program.[11] In this update they indicate new evidence for rt-CGM in pregnant women and the use of SAP in patient subgroups suggests that the original systematic review may not be current.

New evidence comparing rt-CGM vs. SMBG:

- One new RCT (Cordua et al. 2013)[51] observed pregnant women with T1DM using rt-CGM during labor and delivery. In infants of the women involved in the rt-CGM group, approximately 10 (37%) developed neonatal hypoglycemia vs. 27 (46%) in the self-monitoring arm (P = 0.45).

New evidence comparing SAP vs. SMBG:

- One new RCT (Battelino et al. 2011)[52] of 120 children and adults with type 1 diabetes and a HbA1C screening level of <7.5% found that time spent in hypoglycemia was significantly shorter in the rt-CGM group (P = .03), as compared with SMBG. HbA1C at 26 weeks was lower in the rt-CGM group, with a difference of -0.27% (P =0 .008).

SYSTEMATIC REVIEWS (SR'S)

Twelve published SR's[15–26] that examined CGM efficacy and effectiveness were retrieved from our search (see summary in **Table 16**). Meta-analyses of RCTs were conducted in 11 out of the 12 SR's.

The most recent systematic reviews for CGM and those of high quality are discussed in more detail below:

Individual patient Meta-analyses (IPDs): Benkhadra et al. 2017[15] & Pickup et al. 2011[22]

Two systematic reviews included IPD meta-analyses: Benkhadra et al. 2017[15] & Pickup et al. 2011.[22] In contrast to most published meta-analyses that use aggregated data from published reports, the use of individual data allows stronger inferences and reduces the effect of ecological or aggregation bias.

In both IPD meta-analyses HbA1c levels were found to be reduced significantly in T1DM patients treated with rt-CGM compared to SMBG – with similar reductions in HbA1c of -0.30 (95% CI -0.43, -0.17; n=6 RCTs) in Pickup et al. 2011 compared to -0.258 (95% CI -0.464 to -0.052); p=0.014 (n=8 RCTs; all ages with T1DM) in Benkhadra et al. 2017.[15]

In the two step regression model using data from 892 patients by Pickup et al. 2011[22] it was estimated that a patient with T1DM using CGM continuously can expect a reduction in HbA1c of about 0.90% (9 mmol/mol) compared with SMBG when the baseline HbA1c level is 10% (86 mmol/mol); at a baseline HbA1c level of 7% (53 mmol/mol), the reduction with CGM compared with SMBG is about 0.56% (6 mmol/ mol**). It was deemed that a reduction in HbA1c of, for example, 0.9% (9 mmol/mol) in those with an initially high level is associated with a substantial reduced risk of developing diabetic microvascular disease because the relation between absolute risk and HbA1c percentage is curvilinear, with a much larger risk reduction in the high HbA1c range.**

Pickup et al. 2011[22] concluded CGM was associated with a significant reduction in HbA1c percentage, which was greatest in those with the highest HbA1c at baseline and who most frequently used the sensors. Exposure to hypoglycemia was also reduced during CGM therapy. **The authors concluded that the most cost effective or appropriate use of CGM is likely to be when targeted at people T1DM who have continued poor control during intensified insulin therapy and who frequently use CGM.**

Cochrane Systematic review: Langendam et al. 2012[19]

The aim of this Cochrane review was to assess the effects of CGM systems compared to conventional SMBG in patients with T1DM. Twenty-two RCTs were included for review of CGM efficacy and safety. The results of the meta-analyses (across all age groups) indicated benefit of CGM for patients starting on SAP therapy compared to patients using MDI and SMBG. After six months there was a significant larger decline in HbA1c level for real-time CGM users starting insulin pump therapy compared to patients using MDI and SMBG (mean difference (MD) in

change in HbA1c level -0.7%, 95% CI -0.8% to -0.5%, 2 RCTs, 562 patients, I^2=84%). The risk of hypoglycemia was increased for CGM users, but CIs were wide and included unity (4/43 versus 1/35; RR 3.26, 95% CI 0.38 to 27.82 and 21/247 versus 17/248; RR 1.24, 95% CI 0.67 to 2.29). One study reported the occurrence of ketoacidosis from baseline to six months; there was however only one event. Both RCTs were in patients with poorly controlled diabetes.

For patients starting with CGM only, the average decline in HbA1c level six months after baseline was also statistically significantly larger for CGM users compared to SMBG users (MD change in HbA1c level -0.2%, 95% CI -0.4% to -0.1%, 6 RCTs, 963 patients, I^2=55%). On average, there was no significant difference in risk of severe hypoglycemia or ketoacidosis between CGM and SMBG users. The confidence interval however, was wide and included a decreased as well as an increased risk for CGM users compared to the control group. Health-related quality of life was reported in 5/ 22 studies. In none of these studies a significant difference between CGM and SMBG was found. Diabetes complications, death and costs were not measured.[19]

RANDOMIZED CONTROLLED TRIAL (RCTS)

Seventeen RCTs[27–42,43] that examined CGM use in diabetes patients were included in this submission (see **Table 17**). Due to the large amount of level 1 evidence presented, only RCTs with >50 patients and those that utilized Medtronic-specific CGM or SAP systems were included.

The most recent RCTs for CGM and those of relevance to New York diabetic patients are discussed in more detail below:

T1DM

Thirteen RCTs examined CGM use in adults and children with T1DM. In the US/Canadian **Home Closed Loop Study** (Buckingham et al. 2015)[29], 81 children with T1DM were divided into 2 age groups (11–14 and 4–10 years of age) for a 42-night trial. Children were trained to use the MiniMed Paradigm REAL-Time Veo System™ with Enlite™ glucose sensor and were then randomly assigned to either having the system active (intervention night) or inactive (control night). At the end of the trial, median percent time sensor glucose was >70 mg/dL was reduced by 54% from 10.1% (IQR 5.9, 13.8) during control nights to 4.6% on intervention nights (P < 0.001) in 11–14-year-olds (n = 45) and by 50% from 6.2% to 3.1% (P <0.001) in 4–10-year-olds (n = 36). Mean overnight glucose was lower on control versus intervention nights in both age-groups (144 $\pm$ 18 vs. 152 $\pm$ 19 mg/dL [P < 0.001] and 153 $\pm$ 14 vs. 160 $\pm$ 16 mg/dL [P = 0.004], respectively). Mean morning blood glucose was 159 $\pm$ 29 vs. 176 $\pm$ 28 mg/dL (P < 0.001) in the 11–14-year-olds and 154 $\pm$ 25 vs. 158 $\pm$ 22 mg/dL (P = 0.11) in the 4–10-year-olds, respectively. No differences were found between intervention and control in either age-group in morning blood ketosis. The investigators concluded that in 4–14-year-olds, use of a nocturnal predictive low-glucose suspend (PLGS) system can substantially reduce overnight hypoglycemia without an increase in morning ketosis, although overnight mean glucose is slightly higher.

In the **SWITCH**[32] multicenter randomized cross-over study, 153 children and adults on CSII with HbA1c 7.5–9.5% (58.5–80.3 mmol/mol) were randomized to CGM with a Sensor On/or Sensor Off-arm for 6 months. After 4 months washout, participants crossed over to the other arm for 6 months. Pediatric and adult participants were separately electronically randomized through the case report form according to a predefined randomization sequence in eight secondary and tertiary centers. After 6 months the mean difference in HbA1c was –0.43% (–4.74 mmol/mol) in favor of the Sensor On arm (8.04% [64.34 mmol/mol] vs 8.47% [69.08 mmol/mol]; 95% CI −0.32%, −0.55% [−3.50, −6.01 mmol/mol]; p<0.001). While 4 vs 2 events of severe hypoglycemia occurred in the Sensor On and Sensor Off arm, respectively (p=0.40), the investigators conclude this may have been to more frequent self-adjustments of insulin therapy in the Sensor On group.

The **RealTrend study**[40] was a 6-month, randomized, parallel-group, two-arm, open-label study of 132 adults and children with uncontrolled T1DM (HbA1C $\geq$8%) being treated with multiple daily injections. One group was fitted with the Medtronic MiniMed Paradigm REAL-Time™ system (SAP group), with instructions to wear CGM sensors at least 70% of the time. Conventional insulin pump therapy was initiated in the other group (CSII group). A total of 115 patients completed the study. Between baseline and trial end, HbA1c improved significantly in both groups (SAP group -0.81 $\pm$ 1.09%, P< 0.001; CSII group -0.57 $\pm$ 0.94%, P <0.001), with no significant difference between groups. When the 91 patients who were fully protocol-compliant (including CGM sensor wear $\geq$70% of the time) were considered, HbA1c improvement was significantly greater in the SAP group (SAP group -0.96 $\pm$ 0.93%, P < 0.001; CSII group -0.55 $\pm$ 0.93%, P < 0.001). Hyperglycemia parameters decreased in line with improvements in HbA1c with no impact on hypoglycemia. The investigators concluded that CGM-enabled insulin pump therapy improves glycaemia more than conventional pump therapy during the first 6 months of pump use in patients who wear CGM sensors at least 70% of the time.

The pediatric **ONSET study**[37] aimed to examine the use of SAP therapy (Medtronic MiniMed Paradigm REAL-Time™ system) from the diagnosis of childhood T1DM and hypothesized that intensive management early improves subsequent glycemic control and preserves beta-cell function. A total of 160 children (aged 1–16 years, mean ± SD: 8.7±4.4 yrs.) were randomized to receive insulin pump treatment with CGM or conventional SMBG measurements. After 12 months follow-up HbA1c was not significantly different between the CGM vs SMBG groups, but patients with regular sensor use had lower values (mean HbA1c 7.1%, 95% CI 6.8–7.4%) compared with the combined group with no or low sensor usage (mean HbA1c 7.6%, 95% CI 7.3–7.9%; p=0.032). **In addition, glycemic variability at 12 months was lower in the sensor group (mean amplitude of glycemic excursions 80.2±26.2 vs 92.0±33.7; p=0.037).** Severe hypoglycemia was reported only in the group without sensors (four episodes). The authors concluded that SAP therapy starting from the diagnosis of T1DM can be associated with less decline in fasting C-peptide particularly in older children, although regular sensor use is a prerequisite for improved glycemic control.

The **STAR-3 study**[36] was a 1-year, multicenter, randomized open trial that enrolled 485 patients, either adults (329 patients) or children (82, aged 7-12) and adolescents (74, aged 13-18) with uncontrolled T1DM (HbA1c level between 7.4% and 9.5%) despite MDI therapy. Patients were randomized to a SAP with the Medtronic MiniMed Paradigm REAL-Time™ system or to MDI and

SBGM. At baseline, the mean HbA1c, for children and adults, was 8.3% in both study groups. Adult patients experienced HbA1c reduction, showing an improvement in overall glucose control. **The absolute reduction in HbA1c level was 1.0% (SD ± 0.7%) in the SAP therapy group over the 12-month study period**, **as compared to a reduction of 0.4% (SD ± 0.8%) experienced by the MDI group**. The between-group difference favored the SAP therapy group by -0.6% (95% CI, -0.8 to -0.4; P<0.001). The number of adults reaching an HbA1c level of 7% or less was 34% in the SAP therapy group and 12% in the MDI group. Additionally, the STAR 3 clinical trial concluded that an increased frequency of sensor use (i.e., 0 – 100% usage over a 1 year period) was significantly associated with greater reduction in HbA1c levels (P=0.003). These findings are consistent with the meta-regression conducted by Pickup et al. 2011 which concluded that a greater reduction in HbA1c is associated with the number of days per week a patient uses CGM (vs. SMBG).

In the **ASPIRE IN-CLINIC** randomized crossover study[33], 50 subjects used a SAP system with a low glucose suspend (LGS) feature that automatically stops insulin delivery for 2 hrs following a sensor glucose (SG) value $\leq$ 70mg/dL. Subjects fasted overnight and exercised until their plasma glucose value reached $\leq$ 85mg/dL on different occasions separated by washout periods lasting 3–10 days. Exercise sessions were done with the LGS feature turned on (LGS-On) or with continued insulin delivery regardless of SG value (LGS-Off). The order of LGS-On and LGS-Off sessions was randomly assigned. The mean $\pm$ SD hypoglycemia duration was less during LGS-On than during LGS-Off sessions (138.5 $\pm$ 76.68 vs. 170.7 $\pm$ 75.91 min, P = 0.006). During LGS-On compared with LGS-Off sessions, mean glucose was higher (59.5 $\pm$ 5.72 vs. 57.6 $\pm$ 5.69 mg/dL, P = 0.015), as was mean end-observation glucose (91.4 $\pm$ 41.84 vs. 66.2 $\pm$ 13.48 mg/dL, P < 0.001). Most (53.2%) end-observation glucose values in LGS-On sessions were in the 70–180 mg/dL range, and none was > 250 mg/dL. **The investigators concluded that automatic suspension of insulin delivery significantly reduced the duration and severity of induced hypoglycemia without causing rebound hyperglycemia.**

The **ASPIRE IN-HOME** study[30] randomly assigned 247 patients with T1DM and documented nocturnal hypoglycemia to receive SAP therapy with (n=121) or without (n=126) the threshold-suspend (TS) feature for 3 months. While the changes in HbA1c values were similar in the two groups, the mean area under the curve (AUC) for nocturnal hypoglycemic events was 37.5% lower in the TS group than in the control group. Nocturnal hypoglycemic events occurred 31.8% less frequently in the TS group than in the control group (1.5±1.0 vs. 2.2±1.3 per patient week, P<0.001).

CGM use in T2DM & pregnant women

Two RCTs[39,42] examined CGM use in adults with T2DM, while four RCTs[27,28,31,43] examined CGM use in pregnant women with a diagnosis of gestational diabetes mellitus (GDM) or with T1DM or T2DM. The details of these included studies are shown in **Appendix D**.

Economic Value of CGM Technologies

Published economic evaluations have shown that rt- CGM has the potential to substantially reduce healthcare costs by helping patients prevent hypoglycemia and diabetic ketoacidosis.[44–46] A recent US modeling study estimated that rt- CGM could reduce annual hospitalizations for hypoglycemia by 32%, which would reduce associated costs by $54 million in a hypothetical population of 46,500 T1D patients.[44] Another study conducted in Australia demonstrated an incremental cost-effectiveness ratio (ICER) of $18,257 (AUS dollars) per severe hypoglycemic event avoided.[53]

Newest CGM Technologies: Hybrid Closed Loop System (HCL)

The HCL insulin delivery technology uses a control algorithm to automatically increase, decrease, and suspend insulin delivery using subcutaneous glucose sensor data, to improve glucose control and lessen the burden of diabetes management. The most recent trial (Garg et al 2017[54]) using the Medtronic MiniMed 670G insulin pump with HCL algorithm and Guardian Sensor 3 was conducted at 10 sites (9 in the United States and 1 in Israel) and enrolled 129 adolescents and adults with T1DM. After 3 months, HbA1c levels decreased from 7.7% to 7.1% ($P < 0.001$) and from 7.3% to 6.8% ($P < 0.001$, Wilcoxon signed-rank test), in adolescents and adults respectively. The proportion of overall in-target (71–180 mg/dL) sensor glucose (SG) values increased from 60.4% to 67.2% ($P < 0.001$) in adolescents and from 68.8% to 73.8% ($P < 0.001$) in adults. The ability of this integrated system to automatically and safely increase, decrease, and suspend insulin delivery represents an important advance in type 1 diabetes therapy for individuals with diabetes, their families, and their healthcare teams.

b) Please disclose all potential harms or other safety concerns regarding this service (e.g., side effects, adverse effects).

The most relevant potential harms in the literature associated with CGM systems are listed in the PICO criteria on **page 4**, and rates are provided in the outcome analysis. Rates of local and systemic adverse events reported in RCTs are extremely low, as shown in **Table 11** and **Table 12.** Adult all-cause mortality was not reported in any of the included HTAs or systematic reviews.

All known safety and/or device performance information are known to include: *Allergic reaction; Appearance of freckle-like dot where needle is inserted; Bleeding; Bruising; Discomfort; Fainting secondary to needle insertion; Infection; Irritation from tapes used with glucose-sensing products; Minimal blood splatter associated with sensor needle removal ; Pain; Raised bump; Rash; Residual redness associated with adhesive and or tapes; Scarring; Skin irritation or reaction to adhesives; Soreness or tenderness; Swelling at insertion site, sensor fracture, breakage or damage.*

3. The service must improve the net health outcome of a population.

a) How would this service increase the health of New York State Medicaid patients?

Diabetes prevalence in New York is high. For the three years ending in 2013, according to federal government data, approximately 1.6 million adult New Yorkers a year had been diagnosed with diabetes. The cost of treating these patients is high. The Department of Health reports the overall annual cost of diabetes in New York, attributable to both direct medical costs and lost productivity, is $12 billion for all payers, including Medicaid[48].

Robust Level 1 evidence from systematic reviews have shown CGM technology reduces hypoglycemic events more than other treatments, without any differences in other outcomes, including changes in HbA1c levels.[22,24] More importantly, the addition of CGM to CSII and integrated SAP therapy is superior to MDI/SMBG in lowering HBA1c.[19] Thus, the addition of this monitoring method to SMBG and intensive insulin therapy can assist in achieving glycemic targets in individuals with T1DM.

Thus SAP fully integrated therapy can better manage diabetes for the most challenging Medicaid enrollees, particularly those with multiple chronic conditions, including behavioral health issues, housing and substance issues, etc., who may as a result have difficulty performing regular MDI and glucose monitoring that leads to complications, which can dramatically help reduce hospitalizations and re-admissions.

In 2016, the *American Association of Clinical Endocrinologists* and *the American College of Endocrinology* (AACE/ACE) released a Consensus Statement on CGM use in the USA.[48] They concluded that **"*CGM improves glycemic control, reduces hypoglycemia, and may reduce overall costs of diabetes management. Expanding CGM coverage and utilization is likely to improve the health outcomes of people with diabetes*".**

4. The service must be at least as beneficial as any established alternatives.

a) How is this service (1) different from, and (2) more effective than services that currently address the medical conditions for which this service is intended for use?

(1) Conventional SMBG is achieved by obtaining a finger-capillary blood sample, where the blood glucose is usually measured employing a small handheld device - a blood glucose meter. This provides a value of the blood glucose at the moment when the blood was sampled. Although this method has been found to provide an accurate estimate of the glucose level, marked fluctuations in blood glucose can be missed, hampering optimal glycemic control (see **Figure 1**).[55] Continuous glucose monitoring measures interstitial fluid every 5 minutes and provides up to 288 glucose readings per day. This gives a more accurate pattern of daily glucose fluctuations allowing identification of the glycemic effect of

food, physical activity, insulin and different medication types and doses aiding in better self-management with avoiding unrecognized hypoglycemia.[56]

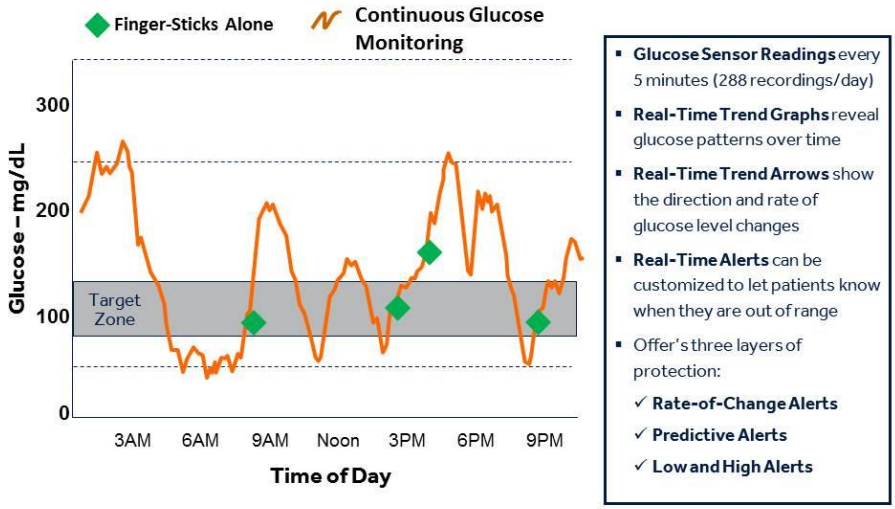

Figure 1: CGM versus SMBG (finger stick)

(2) Studies have shown SMBG is less effective at controlling HbA1c than continuous glucose monitoring. SMBG fails to detect nocturnal hypoglycemia and asymptomatic hypoglycemia even in patients with good control of HbA1c values and it needs multiple blood samples throughout the day.

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b) How does the safety of this service compare with other services that are currently used to treat the medical conditions in question?

Both CGM and SMBG are safe methods to monitor blood glucose levels. While considered safe, SMBG requires a number of finger punctures per day to assess the glucose concentration. Many patients find the multiple finger punches that SMBG requires uncomfortable and painful.[19,57] Challenges that affect adherence to SMBG include pain, costs, behavioral and technical skills, motivation, and intrusiveness.

c) If this is a diagnostic service, what is the current best diagnostic strategy (i.e., diagnostic gold standard), and how does this service compare with it?

CGM is not a diagnostic technology as it does not diagnose diabetes in previously undiagnosed patients. Continuous glucose monitoring is an important component of managing normal blood glucose in IDDM patients.

5. The improvement must be attainable outside of the investigational settings.

a) Please specify which submitted references discuss the clinical effectiveness of the service and its effect on health outcomes outside the investigational setting (e.g., in general community medical practice, among populations with known co-morbidities).

The nature of CGM is such that patients wear the device and collect data continuously outside of in-patient or clinic times. Included studies have shown CGM improves health outcomes in home-based settings[29,30,52] and in patients with poorly controlled diabetes.[36,40,42]

In addition, the US T1D Exchange Clinic Network registry database provides the opportunity to understand the real world characteristics of CGM device use in a large clinic-based population.[58,59] A recent analysis of 17,317 participants in the T1 Exchange registry found CGM use was associated with lower HbA1c in children (8.3% vs. 8.6%, $P < 0.001$) and adults (7.7% vs. 7.9%, $P < 0.001$). In adults, more frequent use of CGM ($\geq$6 days/week) was associated with lower mean HbA1c.[59]

6. The service must be cost-effective or cost neutral outside the investigational setting.

a) What is the total cost for the service (e.g., costs of related physician services or outpatient hospital charges or other services that patients using the service will need)? Please include both initial costs and estimated lifetime costs.

Table 1: Payer and patient first year & Lifetime cost scenario

CGM type	**Payer and Patient Total Cost (1 year)**
Personal CGM	Payer and Patient Total Cost for 1 year (the lifetime of the CGM transmitter): $2,500-$3,500 per year. This cost includes the cost of the consumable sensor, durable transmitter and durable receiver. There are no hospital impacts, professional services, diagnostic services, or other ancillary costs associated with personal CGM therapy.
Professional CGM	Payer and Patient Total Cost for 1 year: $200-$400 per year. Professional CGM is reimbursed via CPT codes 95250 and 95251 directly to the physician and is routinely covered 1 to 2 times per year, and up to once per month. There are no DME costs, capital expenditures for the payer, or ancillary services associated with Professional CGM.

b) Please compare the total cost of the service with the cost of established services that currently address the medical conditions for which this service is intended for use? Please include both initial costs and estimated lifetime costs.

Table 2: CGM versus comparator first year & Lifetime cost scenario

CGM type	**Payer and Patient Total Cost (per year)**
Personal CGM	Cost of MDI and SMBG without Personal CGM (the standard of care) is $22,000-$25,000 per patient year. When adding Personal CGM, the costs are $25,000 to $27,000 per patient per year. This is based on 1 year of all medical costs for the patient including inpatient, outpatient and pharmacy costs from healthcare claims data and includes the payer and patient out of pocket responsibility. The warranty of core parts of the device is one year. There is very limited published, peer-reviewed scientific evidence estimating the lifetime cost of adding Personal CGM for management of an individual patient in the US.
Professional CGM	Cost of SMBG therapy for 1 year is approximately $650-$750 per year. Professional CGM may increase the cost slightly for the patient's monitoring of diabetes, however, analysis of healthcare claims data suggests that, when compared to use of people using SMBG with CGM, use of Professional CGM is not associated with statistically significant differences in cost. There is currently no published, peer-reviewed scientific evidence estimating the lifetime cost of patients using Professional CGM for an individual patient in the US.

7. Other payer coverage of the service.

a) Which State Workers' compensation programs and private Health Plans nationwide cover the use of this service, and have there been any Centers for Medicare or Medicaid Services national or local coverage determinations?

- Commercial: 93% of private insurance carriers cover Personal & Professional CGM
- Medicare – Professional CGM is covered by all Medicare Administrative Contractors as reasonable and necessary
- Medicaid – 31 states

b) Are there any restrictions of this coverage? If yes, please list.

- Personal – Typically covered for people with type 1 diabetes and insulin-requiring type 2 diabetes
- Professional – Covered for diagnosis of diabetes and adjusting diabetes therapy (type 1 or type 2 diabetes)

References & Quality Appraisal Ratings

Please provide an alphabetical list (by last name of first author) of all references included in the dossier submission and the respective methodological quality appraisal ratings for each study. Every study must be assessed using the respective Quality Appraisal Checklists (provided below). See the *Dossier Methods Guidance* document for further information on appraising studies for methodological quality.

Table 3 Appraisal ratings of CGM references used in the submission

Reference	Study Design[1]	Methodological Quality Appraisal Rating (Good, Fair, Poor)
1. Alfadhli, E., Osman, E., and Basri, T., 2016, Use of a real time continuous glucose monitoring system as an educational tool for patients with gestational diabetes *Diabetology and Metabolic Syndrome*, v. 8:48.	*RCT*	*Good*
2. Battelino T, Phillip M. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011;34(4):795-800. doi:10.2337/dc10-1989	*RCT**	*Good*
3. Battelino, T., Conget, I., Olsen, B., SchÃ¼tz-Fuhrmann, I., Hommel, E., Hoogma, R., Schierloh, U., Sulli, N., and Bolinder, J., 2012, The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomized controlled trial: *Diabetologia*, v. 55, p. 3155-3162.	*RCT*	*Good*
4. Benkhadra, K., Alahdab, F., Tamhane, S., Wang, Z., Prokop, L. J., Hirsch, I. B., Raccah, D., Riveline, J. P., Kordonouri, O., and Murad, M. H., 2017, Real-time continuous glucose monitoring in type 1 diabetes: a systematic review and individual patient data meta-analysis: *Clinical Endocrinology*, v. 86, p. 354-360	*Systematic Review*	*Good*
5. Bergenstal, R. M., Tamborlane, W. V., Ahmann, A., Buse, J. B., Dailey, G., Davis, S. N., Joyce, C., Peoples, T., Perkins, B. A., Welsh, J. B., Willi, S. M., and Wood, M. A., 2010, Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes: *New England Journal of*	*RCT*	*Good*

Medicine, v. 363, p. 311-320		
6. Bergenstal, R. M., Klonoff, D. C., Garg, S. K., Bode, B. W., Meredith, M., Slover, R. H., Ahmann, A. J., Welsh, J. B., Lee, S. W., and Kaufman, F. R., 2013, Threshold-based insulin-pump interruption for reduction of hypoglycemia: *N. Engl. J Med*, v. 369, p. 224-232	*RCT*	*Good*
7. Boland E, Monsod T, Delucia M, Al. E. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care. 2001;24(11):1858–1862.	*Single arm interventional**	*Fair*
8. Bronstone A, Graham C. The Potential Cost Implications of Averting Severe Hypoglycemic Events Requiring Hospitalization in High-Risk Adults With Type 1 Diabetes Using Real-Time Continuous Glucose Monitoring. J Diabetes Sci Technol. 2016;10(4):905-913. doi:10.1177/1932296816633233.	*Economic Evaluation**	*Fair*
9. Bukara-Radujkovic, G., Zdravkovic, D., and Lakic, S., 2011, Short-term use of continuous glucose monitoring system adds to glycemic control in young type 1 diabetes mellitus patients in the long run: a clinical trial: *Vojnosanitetski Pregled*, v. 68, p. 650-654.	*RCT*	*Fair*
10. Buckingham, BA; Raghinaru,D; Cameron,F; Bequette, BW; Chase, HP; Maahs,DM; Slover, R; Wadwa, RW et al. 2015. Predictive Low-Glucose Insulin Suspension Reduces Duration of Nocturnal Hypoglycemia in Children Without Increasing Ketosis. *Diabetes Care;*38:1197–1204.	*RCT*	*Good*
11. Chetty, V. T., Almulla, A., Odueyungbo, A., and Thabane, L., 2008, The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in Type I diabetic patients: A systematic review: *Diabetes Research and Clinical Practice*, v. 81, p. 79-87.	*Systematic Review*	*Good*
12. Cordua S, Secher AL, Ringholm L, Damm P, Mathiesen ER. Real-time continuous glucose monitoring during labour and delivery in women with Type 1 diabetes - observations from a randomized controlled trial. Diabet Med. 2013;30(11):1374-1381. doi:10.1111/dme.12246.	*RCT**	*Good*
13. Dinapoli TP. Diabetes in New York State. New York; 2015. https://www.osc.state.ny.us/reports/health/diabetes_2015.pdf .	*Report**	*Not Applicable*
14. ECRI Institute. Threshold suspend Insulin Delivery Systems for Managing Hypoglycemia in Patients with Type 1 Diabetes Mellitus. HTA Inf Serv. 2016;(July):1-48	*HTA*	*Good*
15. Floyd, B., Chandra, P., Hall, S., Phillips, C., Alema-Mensah, E., Strayhorn, G., Ofili, E. O., and Umpierrez, G. E., 2012, Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus: *Journal of Diabetes Science*	*Systematic Review*	*Good*

and Technology, v. 6, p. 1094-1102.		
16. Fonseca VA, Grunberger G, Anhalt H, et al. Continuous Glucose Monitoring: a Consensus Conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. Endocr Pract. 2016;22(8):1008-1021. doi:10.4158/EP161392.CS.	*Consensus conference report**	*Not Applicable*
17. Fonda SJ, Graham C, Munakata J, Powers JM, Price D, Vigersky RA. The Cost-Effectiveness of Real-Time Continuous Glucose Monitoring (RT-CGM) in Type 2 Diabetes. J Diabetes Sci Technol. 2016;10(4):898-904. doi:10.1177/1932296816628547.	*Economic Evaluation**	*Good*
18. Gandhi, G. Y., Kovalaske, M., Kudva, Y., Walsh, K., Elamin, M. B., Beers, M., Coyle, C., Goalen, M., Murad, M. S., Erwin, P. J., Corpus, J., Montori, V. M., and Murad, M. H., 2011, Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials: *Journal of Diabetes Science and Technology*, v. 5, p. 952-965.	*Systematic Review*	*Fair*
19. Garg, S., Brazg, R. L., Bailey, T. S., Buckingham, B. A., Slover, R. H., Klonoff, D. C., Shin, J., Welsh, J. B., and Kaufman, F. R., 2012, Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study: *Diabetes Technology and Therapeutics*, v. 14, p. 205-209.	*RCT*	*Good*
20. Garg SK, Weinzimer SA, Tamborlane W V., et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017;19(3):1-9. doi:10.1089/dia.2016.0421.	*Single arm interventional**	*Good*
21. Golden SH, Brown T, Yeh HC, Maruthur N, Ranasinghe P, Berger Z, Suh Y, Wilson LM, Haberl EB, Bass EB. Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Comparative Effectiveness Review No. 57. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA-290-2007-10061-I.) ***AHRQ Publication No****. 12-EHC036-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm* 22. Golden S, Sapir T. Methods for Insulin Delivery and Glucose Monitoring in Diabetes: Summary of a Comparative Effectiveness Review. J Manag Care Pharm. 2012;18(6):S1-S17. 23. Yeh, H. C., Brown, T. T., Maruthur, N., Ranasinghe, P., Berger, Z., Suh, Y. D., Wilson, L. M., Haberl, E. B., Brick, J., Bass, E. B., and Golden, S. H., 2012, Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: A	*HTA#*	*Good*

systematic review and meta-analysis: *Annals of Internal Medicine,* v. 157, p. 336-347 24. AHRQ. AHRQ Systematic Review Surveillance Program: CER #57: Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. 2016. https://effectivehealthcare.ahrq.gov/ehc/products/242/2182/insulin-blood-sugar-surveillance-160215.pdf.		
25. Golicki, D. T., Golicka, D., Groele, L., and Pankowska, E., 2008, Continuous Glucose Monitoring System in children with type 1 diabetes mellitus: a systematic review and meta-analysis: *Diabetologia,* v. 51, p. 233-240.	*Systematic Review*	*Good*
26. Hermanides J, Nørgaard K, Bruttomesso D, et al. Sensor-augmented pump therapy lowers HbA1c in suboptimally controlled Type1 diabetes; a randomized controlled trial. *Diabet Med*. 2011;28(10):1158-1167.	*RCT*	*Good*
27. Hirsch, I. B., Abelseth, J., Bode, B. W., Fischer, J. S., Kaufman, F. R., Mastrototaro, J., Parkin, C. G., Wolpert, H. A., and Buckingham, B. A., 2008, Sensor-augmented insulin pump therapy: Results of the first randomized treat-to-target study: *Diabetes Technology and Therapeutics,* v. 10, p. 377-383	*RCT*	*Good*
28. Hoeks, L. B. E. A., Greven, W. L., and de Valk, H. W., 2011, Real-time continuous glucose monitoring system for treatment of diabetes: A systematic review: *Diabetic Medicine,* v. 28, p. 386-394.	*Systematic Review*	*Good*
29. IQWiG Reports. 25 March 2015 Continuous interstitial glucose monitoring (CGM) with real-time measurement devices in insulin-dependent diabetes mellitus [English Executive Summary] – Commission No. D12-01*https://www.iqwig.de/download/D12-01_Executive-Summary_Continuous-glucose-monitoring-CGM-with-real-time-measurement-devices.pdf* 30. IQWiG. Continuous interstitial glucose monitoring (CGM) with real-time measurement devices in insulin-dependent diabetes mellitus (FINAL REPORT IN GERMAN). Heal Technol Assess Database. 2015;(3). https://www.iqwig.de/download/D12-01_Abschlussbericht_Kontinuierliche-Glukosemessung-mit-Real-Time-Messgeraeten.pdf	*HTA#*	*Good*
31. Kerr D, Fayers K. Continuous real-time glucose monitoring systems: time for a closer look. Pr Diab Int. 2008;25(1):37–41.	*Narrative Review**	*Not applicable*
32. Kordonouri, O., Pankowska, E., Rami, B., Kapellen, T., Coutant, R., Hartmann, R., Lange, K., Knip, M., and Danne, T., 2010, Sensor-augmented pump therapy from the diagnosis of	*RCT*	*Good*

childhood type 1 diabetes: Results of the Pediatric Onset Study (ONSET) after 12 months of treatment: *Diabetologia,* v. 53, p. 2487-2495.		
33. Langendam, M., Luijf, Y. M., Hooft, L., DeVries, J. H., Mudde, A. H., and Scholten, R. J., 2012, Continuous glucose monitoring systems for type 1 diabetes mellitus: *Cochrane.Database.Syst.Rev,* v. 1, p. CD008101.	*Systematic Review*	*Good*
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48. SBU Alert report no 2013-04 Continuous subcutaneous glucose monitoring for diabetes. *www.sbu.se/201304e* 49. Technology SSC on H. Continuous Subcutaneous Glucose Monitoring for Diabetes [Internet]. SBU Syst Rev Summ. 2013;SBU Alert(october):1-3. http://www.sbu.se/globalassets/publikationer/content1/1/continuous-subcutaneous-glucose-monitoring-for-diabetes.pdf	*HTA#*	*Good*

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53. The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986. http://www.nejm.org/doi/pdf/10.1056/NEJM199309303291401	*RCT**	*Good*
54. The Diabetes Control and Complications Trial Research/ Epidemiology of Diabetes Interventions and Complications Study Research Group. Intensive Diabetes Treatment and Cardiovascular disease in Patients with Type 1 diabetes. N Engl J Med. 2005;353(25):2643-2653.	*Prospective Cohort Study**	*Good*
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57. Wojciechowski, P., Rys›, P., Lipowska, A., Gaweska, M., and Malecki, M. T., 2011, Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes: Systematic review and meta-analysis: *Polskie Archiwum Medycyny Wewnetrznej,* v. 121, p. 333-344.	*Systematic Review*	*Good*
58. Wong JC, Foster NC, Maahs DM, et al. Real-time continuous glucose monitoring among participants in the T1D exchange clinic registry. Diabetes Care. 2014;37(10):2702-2709.	*Cohort study**	*Good*

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59. Yoo, H. J., An, H. G., Park, S. Y., Ryu, O. H., Kim, H. Y., Seo, J. A., Hong, E. G., Shin, D. H., Kim, Y. H., Kim, S. G., Choi, K. M., Park, I. B., Yu, J. M., and Baik, S. H., 2008, Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes*: Diabetes Research and Clinical Practice,* v. 82, p. 73-79.	*RCT*	*Good*

*****These are **supporting references** used in this submission. By 'supporting' we refer to the fact that they did not fit our inclusion/exclusion criteria demonstrated by our PICO, however these references were used throughout this submission to support the arguments and provide additional information for Medtronic CGM therapies and therefore these references are deemed necessary for inclusion in this submission. It is also important to note that some of these supporting references were not in fact studies or systematic reviews and therefore although we attempted to critically appraise the quality of these references using the systematic review checklist provided in the *Dossier Methods Guidance* document, these reports were not systematic reviews and therefore providing an overall QA rating is not applicable.

#Several of the included Health Technology Assessment (HTA) reports on CGM included in this submission had two or more references that reported on the same HTA. Please note that quality appraisals were only performed once for each of these HTA's.

Overall Strength of Body of Evidence

Based on the methodological quality appraisal rating for each reference, please provide the overall strength of the evidence for each outcome and harm as specified by the topic description. See the *Dossier Methods Guidance* document for further information on assessing the overall strength of a body of evidence.

The overall strength of the body of evidence for each outcome and harm should be graded as: **High, Moderate, Low, or Very Low**. Where there is no evidence for an outcome, please list as "N**one**."

NOTE: Please complete this section after completing the individual Quality Appraisal Checklist(s) for each study.

Table 4 Overall strength of the evidence.

Outcome	**Overall Strength of Body of Evidence** *(e.g., High, Moderate, Low, Very Low)*	**Rating Rationale** (*Please discuss study design and quality. Note any inconsistencies, indirectness, imprecision, and publication bias in results.)*
Outcome #1: Change in HbA1c (Glycated hemoglobin) levels	**High**	Our review of CGM evidence identified 13 systematic reviews/HTA's reporting changes in HbA1c levels (see **Table 6**). The good quality meta-analyses consistently showed statistically significant reductions in HbA1c among type 1 diabetic patients of all ages – for example the Cochrane review by Langendam et al. 2012 reported a weighted mean difference in HbA1c levels -0.68 [-0.82, -0.54]; P < 0.00001 for SAP vs SMBG patients with T1DM (n=2 RCTs included).
Outcome #2: Hyperglycemic events	**Moderate**	Our review of CGM evidence identified 6 systematic reviews/HTA's reporting changes in hyperglycemic events (see **Table 7**). Meta-analyses of RCTs show CGM treated patients consistently show reductions in hyperglycemic events compared to SMBG, including time spent in hyperglycemia. Some of these reductions reach statistical significance.

Outcome #3: Hypoglycemic events	**High**	Our review of CGM evidence identified 9 systematic reviews/HTA's reporting changes in hypoglycemic events (see **Table 8**). Meta-analyses of RCTs show CGM treated patients show reductions in incidence of hypoglycemia compared to SMBG Some of these reductions reach statistical significance.
Outcome #4: Ketoacidotic events	**Moderate**	Three systematic reviews/HTA's report meta-analyses of ketoacidotic events in patients treated with CGM technologies compared to SMBG and other comparators (see **Table 9**).No significant differences in treatment arms were measured and low heterogeneity was observed.
Outcome #5: Health Related Quality of Life	**Moderate**	Three systematic reviews and two RCTs that reported HRQol outcomes for CGM were included in this submission (see **Table 10**) No significant differences in HRQol between treatment arms was identified. No meta-analyses could be performed due to differences in HRQol outcomes measured.

Table 5 Overall strength of the evidence

Outcome	**Overall Strength of Body of Evidence** *(e.g., High, Moderate, Low, Very Low)*	**Rating Rationale** (*Please discuss study design and quality. Note any inconsistencies, indirectness, imprecision, and publication bias in results.)*
Harm #1: Local adverse effects	Moderate	3 RCTs reported local adverse events. 2 RCTs showed more skin AEs in the CGM treatment arms than the SMBG treatment arm. One RCT compared CGM vs a competitor monitor (Glucowatch). The competitor experienced more skin adverse events than Medtronic CGM systems.
Harm #2:: Serious adverse events	Moderate	3 RCTs reported serious adverse events. The SMBG treated patients experienced more SAE's in 2 studies, although no significance testing was undertaken. Definitions of SAE varied.

Harm #3: Pain	Moderate	Only one study reporting pain outcomes was identified in any of the included studies. It is important to note that adverse events such as pain are not common and are expected to be reported rarely.
Harm #4: Mortality (any cause)	Moderate	No deaths due to treatments were identified. 3 RCTs reported deaths during the study period. 2 studies were in GDM patients and reported perinatal mortality due to other factors. 1 RCT reported 1 death in an adult diabetic patient. There were no significant differences between treatment arms.

Net Impact Worksheet

Meta-analyses from Health technology Assessments and/or published Systematic reviews)

Table 6 OUTCOME #1: Change in HbA1c (Glycated hemoglobin) levels

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Riemsma, 2016 **Prepared for NICE HTA UK**	**Medtronic Veo (sensor Augmented Pump therapy)** N=1 RCT; adults T1DM	**Integrated CSII +CGM** N=2 studies adults T1DM	3 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c (95% CI)	0.04 (-0.07 to 0.15); NS
	Medtronic Veo (sensor Augmented Pump therapy) N=1 RCT adults T1DM	**CSII (pump) +SMBG** N=1 study adults T1DM	3 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c (95% CI)	0.41 (-0.31 to 0.13); NS
	Medtronic Veo (sensor Augmented Pump	**SMBG + MDI** N=1 study	3 months	Indirect meta-analysis	-0.43 (-0.95 to 0.10); NS

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	therapy) N=1 RCT adults T1DM	adults T1DM		Weighted Mean Difference (WMD) change in HbA1c (95% CI)	
	Integrated CSII +CGM N=2 RCTs adults T1DM	**CSII (pump)+SMBG** N=1 study adults T1DM	3 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c (95% CI)	0.37 (–0.34 to 1.08)
	Integrated CSII +CGM N=2 RCTs adults T1DM	**SMBG + MDI** N=1 study adults T1DM	3 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c (95% CI)	-0.47 (-0.98 to 0.04)
	Integrated CSII +CGM N=1 RCTs adults T1DM	**CSII (pump)+SMBG** N=1 RCT adults T1DM	6 months	Indirect meta-analysis Weighted Mean Difference	-0.05 (-0.31 to 0.21), NS

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				(WMD) change in HbA1c (95% CI)	
	Integrated CSII +CGM N=1 RCTs adults T1DM	**SMBG + MDI** N=1 study adults T1DM	6 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c (95% CI)	-1.10 (-1.46,-0.74) , S
	Integrated CSII+CGM; (Paradigm 722 System, Medtronic) (1 RCT; n=49) adults T1DM	**CSII (Paradigm 715 Insulin Pump, Medtronic)+SMBG** (1 RCT; n=49) adults T1DM	6 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up (SE), p value	–0.0364 (SE 0.1412); p = 0.80
	Integrated CSII+CGM (MiniMed Paradigm REAL-Time 722 System) (1 RCT; n=14) adults T1DM Baseline HbA1c, % (SD): 8.87 (0.89) Follow-up HbA1c, % :	**MDI + SMBG** (1 RCT; n=13) adults T1DM Baseline HbA1c, % (SD): 8.32 (1.05), Follow-up HbA1c, % : 7.30 (0.92)	3 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up, p value	–0.69; p = 0.071

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	7.16 (0.75)				
	Integrated CSII+CGM (MiniMed Paradigm REAL-Time 722 System) (1 RCT; n=8) adults T1DM Baseline HbA1c, % (SD): 9.45 (0.55) Follow-up HbA1c, % : 7.40 (0.66)	**MDI + SMBG** (1 RCT; n=8) adults T1DM Baseline HbA1c, % (SD): 8.58 (1.30) Follow-up HbA1c, % : 7.50 (1.01)	3 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up, p value	–0.97; p = 0.02
	Integrated CSII+CGM (MiniMed Paradigm REAL-Time 722 System) (1 RCT; n=41) adults T1DM Baseline HbA1c, % (SD): 8.46 (0.95) Follow-up HbA1c, % : 7.23 (0.65)	**MDI + SMBG** (1 RCT; n=36) adults T1DM Baseline HbA1c, % (SD): 8.59 (0.82) Follow-up HbA1c, % : 8.46 (1.04)	6 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up, (95% CI)	-1.1 (-1.47 to -0.73)
	Integrated CSII+CGM (MiniMed Paradigm REAL-Time 722 System) (1 RCT; n=169) adults T1DM	**MDI + SMBG** (1 RCT; n=167) adults T1DM Baseline HbA1c, % (SD): 8.3 (0.5)	12 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up,	–0.6, (-0.8 to -0.4) p < 0.001

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Baseline HbA1c, % (SD): 8.3 (0.5) Follow-up HbA1c, % : 7.3 (NR)	Follow-up HbA1c, % : 7.9 (NR)		(95% CI), p value	
	MiniMed Veo system (1 RCT; n=46); mixed population T1DM Baseline HbA1c, % (95%CI): 7.6 (7.4-7.9) Follow-up HbA1c, % (95%CI): 7.5 (7.3- 7.7)	**CSII+SMBG** (1 RCT; n=49); mixed population T1DM Baseline HbA1c, % (95%CI): 7.4 (7.2-7.6) Follow-up HbA1c, % (95%CI): 7.4 (7.2 - 7.7)	6 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up, (95% CI), p value	0.07 (–0.2 to 0.3); p = 0.55
	MiniMed Veo system (1 RCT); children with T1DM	**Integrated CSII+CGM** (1 RCT); children with T1DM	6 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c(95% CI)	0.38 (-0.16 to 0.92)
	MiniMed Veo system (1 RCT); children with T1DM	**CSII+SMBG** (1 RCT); children with T1DM	6 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c(95%	-0.04 (-0.26 to 0.18)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				CI)	
	Integrated CSII+CGM (1 RCT); children with T1DM	**CSII+SMBG** (1 RCT); children with T1DM	6 months	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c(95% CI)	-0.42 (-0.92 to 0.08)
	Integrated CSII+CGM (1 RCT; n=17); children with T1DM Baseline HbA1c, % (SD): 8.82 (1.05) Follow-up HbA1c, % (SD): 8.02 (1.11)	**CSII+SMBG** (1 RCT; n=23); children with T1DM Baseline HbA1c, % (SD): 8.59 (0.80) Follow-up HbA1c, % (SD): 8.21 (0.97)	6 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up, (SE); p value	0.489 (SE 0.2899); p = 0.10
	Integrated CSII+CGM (1 RCT; n=78); children with T1DM Baseline HbA1c, % (SD): 8.3 (0.6) Follow-up HbA1c, % (SD): 7.9 (NR)	**MDI + SMBG** (1 RCT; n=81); children with T1DM Baseline HbA1c, % (SD): 8.3 (0.5) Follow-up HbA1c, % (SD): 8.5 (NR)	12 months	Direct meta-analysis Mean change in HbA1c levels from baseline to follow-up, (95% CI), p value	-0.5 (-0.8 to -0.2); p < 0.001
	MiniMed Veo system (1 RCT); adults and	**MDI + SMBG** (1 RCT); adults and	All follow-up times	Indirect meta-analysis	-0.66 (-1.05 to -0.27)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	mixed populations T1DM	mixed populations T1DM		Weighted Mean Difference (WMD) change in HbA1c(95% CI)	
	Integrated CSII+CGM (4 RCTs); adults and mixed populations T1DM	**MDI + SMBG** (4 RCTs); adults and mixed populations T1DM	All follow-up times	Indirect meta-analysis Weighted Mean Difference (WMD) change in HbA1c(95% CI)	-0.70 (-1.05, -0.30) This result was from a random-effects analysis as I^2 was 62.5%.
AHRQ 2012 USA HTA [full rpt in Golden 2012]	**RT-CGM** (7 RCTs) Children & adolescents with T1DM	**SMBG** (7 RCTs) Children & adolescents with T1DM	Min 12 weeks	Direct Meta-analysis Weighted Mean Difference (WMD) change in HbA1c(95% CI)	-0.26 (-0.46, -0.06) S
	RT-CGM (4 RCTs) adults with T1DM	**SMBG** (4 RCTs) adults with T1DM	Min 12 weeks	Direct Meta-analysis Weighted Mean Difference	-0.30 (-0.37, -0.22) S

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				(WMD) change in HbA1c(95% CI)	
	RT-CGM (4 RCTs) adults with T1DM; with CGM compliance >60%	**SMBG** (4 RCTs) adults with T1DM	Min 12 weeks	Sensitivity analyses Weighted Mean Difference (WMD) change in HbA1c(95% CI)	-0.36; (-0.44, -0.27) S
	SAP (MM Paradigm REALTime System) (4 RCTs) Children and adults with T1DM	**MDI +SMBG** (4 RCTs) Children and adults with T1DM	Follow-up 15 weeks to 1 year.	Direct Meta-analysis Weighted Mean Difference (WMD) change in HbA1c(95% CI); p value	-0.68 (-0.81, -0.54); P < 0.001
Benkhadra 2017 **Systematic review**	**RT-CGM** (8 RCTs; N=1371) Children, adolescents & adults with T1DM	**Control group** (8 RCTs; N=1371) Children, adolescents & adults with T1DM	NR	Individual patient data (IPD) Meta-analysis HbA1c(95% LL, UL)	-0.258 (-0.464 to -0.052); p=0.014 I^2 value = 83%.
	RT-CGM (9 RCTs; N=1433)	**Control group** (9 RCTs; N=1433)	NR	Meta-analysis including IPD &	-0.276 (-0.465 to -0.087); P=

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Children, adolescents & adults with T1DM	Children, adolescents & adults with T1DM		aggregate patient data HbA1c(95% LL, UL)	0.004 I^2 value = 82%. This is one-stage model that includes aggregate data from a trial that did not provide individual patient data.
	RT-CGM (7 RCTs; N=291) Age≤12; T1DM	**Control group** (7 RCTs; N=291) Age≤12; T1DM	NR	Individual patient data (IPD) Meta-analysis; HbA1c(95% LL, UL)	-0.047 (-0.217 to -0.124); p= 0.592
	RT-CGM (7 RCTs; N=178) Age 13-15; T1DM	**Control group** (7 RCTs; N=178) Age 13-15; T1DM	NR	Individual patient data (IPD) Meta-analysis; HbA1c(95% LL, UL)	-0.039 (-0.320 to 0.242); p= 0.787
	RT-CGM (7 RCTs; N=902) Age >15; T1DM	**Control group** (7 RCTs; N=902) Age >15; T1DM	NR	Individual patient data (IPD) Meta-analysis;	-0.356 (-0.551 to -0.160); p<0.001

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				HbA1c(95% LL, UL)	
Matsuda 2014 **Systematic review**	**CGM + CSII** (2 RCTs; N=41) T1DM in adolescents (ages 12-18)	**SMBG +CSII** (2 RCTs; N=44) T1DM in adolescents (ages 12-18)	26 weeks	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.11 (-0.61 to 0.39); P=0.67 Chi2=0.14,P=0.7
Poolsup 2013 **Systematic review**	**CGM (Real Time and retrospective)** (10 RCTs; N=413) T1DM in children	**SMBG** (10 RCTs; N=404) T1DM in children	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.13% (-0.38 to 0.11%); p = 0.27) Heterogeneity I^2=71%; p=0.0003
	CGM (retrospective) (5 RCTs; N=97) T1DM in children	**SMBG** (5 RCTs; N=87) T1DM in children	All follow-up times	Sensitivity analysis Weighted mean difference (95% CI) in HbA1c	-0.05% (-0.46 to 0.35%); p = 0.79) Heterogeneity I^2=72%; p=0.007
	RT-CGM (real time) (5 RCTs; N=316) T1DM in children	**SMBG** (5 RCTs; N=317) T1DM in children	All follow-up times	Sensitivity analysis Weighted mean	-0.18% (-0.35 to -0.02%); p = 0.02) Heterogeneity

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				difference (95% CI) in HbA1c	I^2=48%; p=0.02
Langendam 2012 **Systematic review**	**CGM augmented pump therapy** (2 RCTs; n=285) T1DM	**SMBG** **(2 RCTs; n=277)** T1DM	6 months	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.68 [-0.82, -0.54]; P < 0.00001 Heterogeneity I^2=84%; p=0.01
	CGM augmented pump therapy (1 RCT; n=244) T1DM	**SMBG** (1 RCT; n=241) T1DM	12 months	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.60 [-0.75, -0.45]; P < 0.00001
	RT-CGM **(8 RCTs; N=482)** Adults & children with T1DM	**SMBG** **(8 RCTs; N=481)** Adults & children with T1DM	6 months	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.23 [-0.36, -0.09]; P = 0.00083 Heterogeneity I^2=55%; p=0.03
	RT-CGM (1 RCT; N=76)	**SMBG** (8 RCTs; N=78)	12 months	Direct meta-analysis	0.10 [-0.46, 0.66]; P=0.73

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Adults & children with T1DM	Adults & children with T1DM		Weighted mean difference (95% CI) in HbA1c; p value	
	Intermittent Real-time CGM (4 RCTs; N=107) Adults & children with T1DM	**SMBG (4 RCTs; N=109)** Adults & children with T1DM	3 months	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.18 [-0.42, 0.05]; P=0.13 Heterogeneity I^2=0%; p=0.64
Floyd 2012 **Systematic review**	**All types of CGM** (14 RCTs) 1188 participants Adults & children with T1DM	**SMBG** (14 RCTs) 1188 participants Adults & children with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.28 [-0.37, -0.19]; p < .0001
	Retrospective CGM (8 RCTs) Adults & children with T1DM	**SMBG** (8 RCTs) Adults & children with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.3 [-0.4, -0.2] ; P<0.0001
	Real-time CGM	**SMBG**	All follow-	Direct meta-	-0.3 [-0.5, -0.2] ;

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	(8 RCTs) Adults & children with T1DM	(8 RCTs) Adults & children with T1DM	up times	analysis Weighted mean difference (95% CI) in HbA1c; p value	P<0.0001
Szypowska 2012 **Systematic review**	**Real-time CGM** (7 RCTs; 948 subjects) Adults & children with T1DM	**SMBG** (7 RCTs; 948 subjects) Adults & children with T1DM	follow-up period ranged from 3 to 12 months	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	–0.25 (–0.34, –0.17); P<0.001
	Real-time CGM + CSII (4 RCTs; 497 subjects) Adults & children with T1DM	**SMBG** (4 RCTs; 497 subjects) Adults & children with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.26;(-0.43,-0.10); P<0.002
	Real-time CGM (3 RCTs; 224 subjects) Adults with T1DM	**SMBG** (3 RCTs; 224 subjects) Adults with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.37 (-0.76, 0.02; P=0.06 Heterogeneity I^2=77%

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Real-time CGM (3 RCTs; 308 subjects) Children with T1DM	**SMBG** (3 RCTs; 308 subjects) Children with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.19 (-0.42, -0.03); P=0.09
	Real-time CGM (1 RCT; 129 subjects) T1DM Patients with good metabolic control	**SMBG** (1 RCT; 129 subjects) T1DM Patients with good metabolic control	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.31; (-0.46, -0.16); P<0.001
	Real-time CGM (4 RCTs; 603 subjects) T1DM Patients with poor glycemic control	**SMBG** (4 RCTs; 603 subjects) T1DM Patients with poor glycemic control	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.21; (-0.32, -0.09); P<0.001
Wojciechowski 2011 **Systematic review**	**All CGM types** (14 RCTs; n=659) Adults & children with T1DM	**SMBG** (14 RCTs; n=592) Adults & children with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in	–0.26 [–0.34; –0.19]; P<0.0001 Heterogeneity I^2 = 0%; P = 0.94

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				HbA1c; p value	
	Real time CGM (8 RCTs; n=549) Adults & children with T1DM	**SMBG** (8 RCTs; n=496) Adults & children with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c	–0.27 [–0.34; –0.19] Heterogeneity (P = 0.685) I^2 = 0%
	Retrospective CGM (6 RCTs; n=110) Adults & children with T1DM	**SMBG** (6 RCTs; n=96) Adults & children with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c	-0.22 [–0.48; 0.04] Heterogeneity (P = 0.942) I^2 = 0%
	All CGM types (5 RCTs; n=NA) Adults with T1DM	**SMBG** (5 RCTs; n=NA) Adults with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c	–0.33 [–0.46; –0.20] Heterogeneity (P = 0.89) I^2 = 51%
	All CGM types (8 RCTs; n=NA) Children, adolescents with T1DM	**SMBG** (8 RCTs; n=NA) Children, adolescents with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference	–0.25 [–0.43; –0.08] Heterogeneity (P = 0.769) I^2 = 0%

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				(95% CI) in HbA1c	
	All CGM types (5 RCTs; n=NA) Mixed populations with T1DM	**SMBG** (5 RCTs; n=NA) Mixed populations with T1DM	All follow-up times	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c	–0.25 [–0.35; –0.15] Heterogeneity (P = 0.120) I2 = 45%
Pickup 2011 **Systematic review**	**CGM** (6 RCTs; N=449) T1DM, All ages included	**SMBG** (6 RCTs; N=443) T1DM, All ages included	Range: 13 to 26 weeks	IPD meta-analyses Weighted mean difference (95% CI) in HbA1c	-0.30 (-0.43, -0.17) Heterogeneity I^2 = 47.2%; P=0.092
Ghandi 2011 **Systematic review**	**CGM** (RCT number and subjects - NR) T1DM & T2DM, All ages included	**SMBG** (RCT number and subjects - NR) T1DM & T2DM, All ages included	>8 weeks	Random Effects Direct meta-analysis Weighted mean difference (95% UL, LL) in HbA1c;	-0.27 (-0.44, -0.10) Heterogeneity I^2 = 59%
	CGM (4 RCTs, N=146) Adults with T1DM	**SMBG** (4 RCTs, N=141) Adults with T1DM	>8 weeks	Random Effects Direct meta-analysis	-0.50 (-0.69, -0.30)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				Weighted mean difference (95% UL, LL) in HbA1c	
	CGM (3 RCTs, N=61) Adults with T2DM	**SMBG** (3 RCTs, N=67) Adults with T2DM	>8 weeks	Random Effects Direct meta-analysis Weighted mean difference (95% UL, LL) in HbA1c	-0.70 (-1.14, -0.27)
	CGM (3 RCTs, N=153) All ages with T1DM	**SMBG** (3 RCTs, N=153) All ages with T1DM	>8 weeks	Random Effects Direct meta-analysis Weighted mean difference (95% UL, LL) in HbA1c	-0.32 (-0.48, -0.16)
	CGM (7 RCTs, N=307) Children and adolescents with T1DM	**SMBG** (7 RCTs, N=298) Children and adolescents with T1DM	>8 weeks	Random Effects Direct meta-analysis Weighted	-0.06 (-0.31, 0.18)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				mean difference (95% UL, LL) in HbA1c	
Chetty 2008 **Systematic review**	**CGM** (7 RCTs, N=NA) All ages with T1DM	**SMBG** (7 RCTs, N=NA) All ages with T1DM	12-24 weeks	Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	0.22%; (-0.439% to 0.004%), p = 0.055 Heterogeneity I^2 = 0%
	CGM (2 RCTs, N=NA) Adults with T1DM	**SMBG** (2 RCTs, N=NA) Adults with T1DM	12-24 weeks	Random effects Direct meta-analysis Weighted mean difference (95% CI) in HbA1c	-0.1109 (-0.4011, 0.179)
	CGM (5 RCTs, N=NA) Pediatric patients with T1DM	**SMBG** (5 RCTs, N=NA) Pediatric patients with T1DM	12-24 weeks	Random effects Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.3679 (-0.7130, -0.02285); P = 0.036

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	CGM (3 RCTs, N=NA) All ages with T1DM; high quality studies	**SMBG** (3 RCTs, N=NA) All ages with T1DM; high quality studies	12-24 weeks	Random effects Direct meta-analysis Weighted mean difference (95% CI) in HbA1c; p value	-0.0439 (-0.3462, 0.2584); P = 0.775
	CGM (4 RCTs, N=NA) All ages with T1DM; lower quality studies	**SMBG** (4 RCTs, N=NA) All ages with T1DM; lower quality studies	12-24 weeks	Random effects Direct meta-analysis Weighted mean difference (95% CI) in HbA1c	-0.4207 (-0.7481, -0.0934)
Golicki 2008 **Systematic review**	**CGM** (5 RCTs, N=70) Children or adolescents with T1DM	**SMBG** (5 RCTs, N=61) Children or adolescents with T1DM	3-6 months	Fixed effects Direct meta-analysis Weighted mean difference (95% CI) in HbA1c, p value	-0.02 (-0.29, 0.25); p=0.87 Heterogeneity I^2 = 0%; p=0.74

Table 7 OUTCOME #2: Hyperglycemic events (including the frequency of hyperglycemic events; the number of hyperglycemic episodes; the time spent in Hyperglycemia)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Riemsma, 2016 **Prepared for NICE HTA UK**	**Integrated CSII+CGM (SAP)** (1 RCT; n=41); adults T1DM Mean number of Hyperglycemic events (glucose levels of > 11.1 mmol/l) per day (SD) = **2.1 (0.8)**	**MDI+SMBG** (1 RCT; n=36); adults T1DM Mean number of Hyperglycemic events (glucose levels of > 11.1 mmol/l) per day (SD) = **2.1 (0.8)**	6 months	Mean difference in the number of Hyperglycemic events (glucose levels of > 11.1 mmol/l) per day at follow-up (95% CI)	–0.2, (–0.5 to 0.2)
	Integrated CSII+CGM (SAP) (1 RCT; n=169); adults T1DM Hyperglycemic AUC (> 250 mg/dl) at follow-up = **3.74 (5.01)**	**MDI+SMBG** (1 RCT; n=167); adults T1DM Hyperglycemic AUC (> 250 mg/dl) **7.38 (8.62)**	12 months	Difference in Hyperglycemic AUC (> 250 mg/dl) at follow-up	3.64; p< 0.001

	Integrated CSII+CGM (SAP) (1 RCT; n=78); children T1DM Hyperglycemic AUC (> 250 mg/dl) at follow-up = **9.2 (8.08)**	**MDI+SMBG** (1 RCT; n=81); children T1DM Hyperglycemic AUC (> 250 mg/dl) **17.64 (14.62)**	12 months	Difference in Hyperglycemic AUC (> 250 mg/dl) at follow-up	8.44; p< 0.001
AHRQ 2012 **USA** **HTA** **[full rpt in Golden 2012 & Yeh, 2012]**	**Rt-CGM** (4 RCTs; n=78); children T1DM	**SMBG** (4 RCTs; n=78); children T1DM	Median follow-up of all included studies was 24 weeks	Time spent in hyperglycemic range (defined as glucose level greater than 180 mg/dL) Meta-analysis showing Mean between-group difference (95%CI)	-68.56 minutes/day (-101.17 to -35.96); P = 0.326. favoring rt-CGM

	Rt-CGM + CSII (SAP) (2 RCTs)	**SMBG/MDI** (2 RCTs)	Median follow-up of all included studies was 24 weeks	Time spent in hyperglycemic range (defined as glucose level greater than 180 mg/dL) Meta-analysis showing Mean between-group difference (95%CI)	p< 0.001
Langendam 2012 **Cochrane Systematic review**	**Retrospective CGM** (1 RCT; n=18); children with T1DM Mean(SD)[AUC] 662 (229)	**SMBG** (1 RCT; n=9); children with T1DM Mean(SD)[AUC] 656 (243)	3 months	Mean difference in CGM-derived hyper-glycaemia (AUC) Fixed effects meta-analysis (95% CI)	6.00 [-184.78, 196.78]

	Real time CGM (1 RCT; n=78); children with T1DM Mean(SD)[AUC] 39.36 (21.7)	**SMBG** (1 RCT; n=81); children with T1DM Mean(SD)[AUC] 44.68 (20.34)	12 months	Mean difference in CGM-derived hyper-glycaemia (AUC) Random effects meta-analysis (95% CI)	-5.32 [-11.86, 1.22]
	Retrospective CGM (1 RCT; n=51); children with T1DM Mean(SD)[Hyperglycemic Events/day] 2.9 (1.2)	**SMBG** (1 RCT; n=58); children with T1DM Mean(SD)[Hyperglycemic Events/day] 2.8 (1.2)	3 months	Mean difference in CGM-derived hyper-glycaemia events per day Random effects meta-analysis (95% CI)	0.10 [-0.35, 0.55]
	Real time CGM (1 RCT; n=169); adults with T1DM Mean(SD)[AUC] 28.92 (17.8)	**SMBG** (1 RCT; n=167); adults with T1DM Mean(SD)[AUC] 28.04 (17.03)	12 months	Mean difference in CGM-derived hyper-glycaemia (AUC) Random effects meta-analysis (95% CI)	0.88 [-2.84, 4.60]

	Real time CGM (1 RCT; n=40); adults with T1DM Mean(SD)[% time] 2.7 (3.4)	**SMBG** (1 RCT; n=31); adults with T1DM Mean(SD)[% time] 2.5 (3.6)	6 months	Mean difference in CGM-derived hyper-glycaemia (% time in hyperglycemia) Random effects meta-analysis (95% CI)	0.20 [-1.45, 1.85]
Floyd 2012 **Systematic review**	**CGM** (No info on included studies) Duration of hyperglycemia (min/ day BG ≥ 240 mg/dl) 172.26 ± 125.90	**SMBG** (No info on included studies) Duration of hyperglycemia (min/ day BG ≥ 240 mg/dl) 217.53 ± 152.94	All follow-up times	Fixed effects meta-analysis weighted of mean difference [95% CI] in the duration of hyperglycemia (min/ day BG ≥ 240 mg/dl)	-45.3 [-65.5, -25.0] ; p<0.0001
Wojciechowski 2011 **Systematic review**	**CGM** (1 RCT; n=322); Adults & children with T1DM change of time spent in hyperglycemia >10.0 mmol/l (min/day)	**SBGM** (1 RCT; n=322); Adults & children with T1DM change of time spent in hyperglycemia >10.0 mmol/l (min/day)	6 months	Meta-analysis change of time spent in hyperglycemia >10.0 mmol/l (min/day); estimate (95%CI)	–60.52[–101.35; –19.69]

	CGM (1 RCT; n=100); Adults & children with T1DM change of time spent in hyperglycemia >10.5 mmol/l (hrs/day)	**SMBG** (1 RCT; n=100); Adults & children with T1DM change of time spent in hyperglycemia >10.5 mmol/l (hrs/day)	6 months	Meta-analysis change of time spent in hyperglycemia >10.5 mmol/l (hrs/day); mean difference (95%CI)	–2.80 [–4.52; –1.08]
	CGM (1 RCT; n=322); Adults & children with T1DM change of time spent in hyperglycemia >13.9 mmol/l (min/day)	**SMBG** (1 RCT; n=322); Adults & children with T1DM change of time spent in hyperglycemia >13.9 mmol/l (min/day)	6 months	Meta-analysis change of time spent in hyperglycemia >13.9 mmol/l (min/day); mean difference (95%CI)	–29.15 [–45.37; –12.92]
Ghandi 2011 **Systematic review**	**CGM** (1 RCT; n=19); children with T1DM Incidence of hyperglycemia	**SMBG** (1 RCT; n=17); children with T1DM Incidence of hyperglycemia	3 months	Meta-analysis of hyperglycemia events Risk ratio (95% CI)	2.70 (0.12, 62.17)
	CGM (1 RCT); adults & children with T1DM Incidence of hyperglycemia / number of episodes= 4/90	**SMBG** (1 RCT); adults & children with T1DM Incidence of hyperglycemia/ number of episodes = 3/90	NR	Meta-analysis of hyperglycemia episodes Rate ratio (95% CI)	1.33 (0.30, 5.96)

Table 8 OUTCOME #3: Hypoglycemic events (including the frequency of (nocturnal) hypoglycemic events and the number of hypoglycemic episodes, stratified by severity into 'mild' or 'severe' if data were available).

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Riemsma, 2016 **Prepared for NICE HTA UK**	**MiniMed Veo system (SAP with low glucose suspend feature)** (1 RCT; n=121); adults with T1DM Nocturnal hypoglycemic events per patient per week (glucose < 3.6 mmol/l) (SD) = **1.5 (1.0) at follow-up**	**Integrated CSII+CGM (SAP standard)** (1 RCT; n=126); adults with T1DM Nocturnal hypoglycemic events per patient per week (glucose < 3.6 mmol/l) (SD) = **2.2 (1.3) at follow-up**	3 months	Difference at follow-up of nocturnal hypoglycemic events per patient per week (glucose < 3.6 mmol/l ;p value	NR; p < 0.001
	MiniMed Veo system (SAP with low glucose suspend feature) (1 RCT; n=121); adults with T1DM Day and night hypoglycemic events per patient per week (glucose < 3.6 mmol/l) (SD) at follow-up = **3.3 (2.0)**	**Integrated CSII+CGM (SAP standard)** (1 RCT; n=126); adults with T1DM Day and night hypoglycemic events per patient per week (glucose < 3.6 mmol/l) (SD) at follow-up = **4.7 (2.7)**	3 months	Difference at follow-up of nocturnal hypoglycemic events per patient per week (glucose < 3.6 mmol/l ;p value	NR; p < 0.001
	MiniMed Veo system (SAP with low glucose suspend feature) (1 RCT; n=121); adults with	**Integrated CSII+CGM (SAP standard)** (1 RCT; n=126); adults with T1DM	3 months	Difference at follow-up of Nocturnal hypoglycemic	NR; p < 0.001

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	T1DM Nocturnal hypoglycemic AUC[a] (SD) = **980 (1200)**	 Nocturnal hypoglycemic AUC[a] (SD) = **1568 (1995)**		AUC[a]; p value	
	MiniMed Veo system (SAP with low glucose suspend feature) (1 RCT; n=121); adults with T1DM Day and night hypoglycemic AUCa (SD) = **798 (965)**	**Integrated CSII+CGM (SAP standard)** (1 RCT; n=126); adults with T1DM Day and night hypoglycemic AUC[a] (SD) = **1164 (1590)**	3 months	Difference at follow-up of Day and night hypoglycemic AUC[a] p value	NR; p < 0.001
	Integrated CSII+CGM (1 RCT; n=41); adults with T1DM Hypoglycemic events, mean number of events (glucose levels of < 4.0 mmol/l) per day (SD) = **0.7 (0.7)**	**MDI+SMBG** (1 RCT; n=36); adults with T1DM Hypoglycemic events, mean number of events (glucose levels of < 4.0 mmol/l) per day (SD) = **0.6 (0.7)**	6 months	Mean difference at follow-up of Day and night hypoglycemic AUC[a] (95% CI); p value	0.1, (–0.2 to 0.5)
	Integrated CSII+CGM (1 RCT; n=169); adults with T1DM Severe hypoglycemia	**MDI+SMBG** (1 RCT; n=167); adults with T1DM Severe hypoglycemia	12 months	Difference in Severe hypoglycemia between groups	Not significant

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	(patients with hypoglycemic events/total patients) = **17/169**	(patients with hypoglycemic events/total patients) = **13/167**			
Riemsma, 2016 **Prepared for NICE HTA UK** **continued**	**Integrated CSII+CGM** (1 RCT; n=169); adults with T1DM Severe hypoglycemic event rate (per 100 person-years; HbA1c levels < 50 mg/dl) = 15.31/169	**MDI+SMBG** (1 RCT; n=167); adults with T1DM Severe hypoglycemic event rate (per 100 person-years; HbA1c levels < 50 mg/dl) = 17.62/167	12 months	Difference in Severe hypoglycemic event rate; p value	p = 0.66
	Integrated CSII+CGM (1 RCT; n=169); adults with T1DM Hypoglycemic AUC (threshold of < 70 mg/dl) = **0.25 (0.44)**	**MDI+SMBG** (1 RCT; n=167); adults with T1DM Hypoglycemic AUC (threshold of < 70 mg/dl) = **0.29 (0.55)**	12 months	Difference in Hypoglycemic AUC (threshold of < 70 mg/dl); p value	p= 0.63
	Integrated CSII +CGM (3 RCTs; n=NR); adults with T1DM proportion of patients with	**CSII+SMBG** (3 RCTs; n=NR); adults with T1DM proportion of patients with	3 months	Indirect meta-analysis: **Relative Risk (RR) (95% CI)**	0.33 (0.03 to 3.87)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	severe hypoglycemia	severe hypoglycemia			
	Integrated CSII +CGM (2 RCTs; n=NR); adults with T1DM proportion of patients with severe hypoglycemia	**MDI+SMBG** (2 RCTs; n=NR); adults with T1DM proportion of patients with severe hypoglycemia	3 months	Indirect meta-analysis: **Relative Risk (RR) (95% CI)**	0.19 (0.02 to 1.51)
	MiniMed Veo system (1 RCT; n=46); mixed population (mainly children) with T1DM Number of people with hypoglycemic Events = **0/41**	**CSII+SMBG** (1 RCT; n=49); mixed population (mainly children) with T1DM Number of people with hypoglycemic Events = **6/46**	6 months	Difference at follow-up	Not significant
	MiniMed Veo system (1 RCT; n=46); mixed population (mainly children) with T1DM Hypoglycemic incidence rate (The number of hypoglycemic events per 100 patient-months) = **9.5 (95% CI 5.2 to 17.4)**	**CSII+SMBG** (1 RCT; n=49); mixed population (mainly children) with T1DM Hypoglycemic incidence rate (The number of hypoglycemic events per 100 patient-months) = **34.2 (95% CI 22.0 to 53.3)**	6 months	Difference at follow-up **incidence rate ratio (95% CI); p value**	3.6 (1.7 to 7.5); $p < 0.001$
Riemsma, 2016	**Integrated CSII+CGM** (1 RCT; n=78); children with	**MDI+SMBG** (1 RCT; n=81); children with	12 months	Difference in Number of	Not significant

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Prepared for NICE HTA UK **continued**	T1DM Number of people with severe hypoglycemic events (patients with severe hypoglycemic events/total number of patients) = **4/78**	T1DM Number of people with severe hypoglycemic events (patients with severe hypoglycemic events/total number of patients) = **4/81**		people with severe hypoglycemic events at follow up	
	Integrated CSII+CGM (1 RCT; n=78); children with T1DM Severe hypoglycemic event rate (per 100 person-years; HbA1c levels of < 50 mg/dl)= **8.98/78**	**MDI+SMBG** (1 RCT; n=81); children with T1DM Severe hypoglycemic event rate (per 100 person-years; HbA1c levels of < 50 mg/dl) =**4.95/81**	12 months	Difference in Severe hypoglycemic event rate at follow up	P=0.35
	Integrated CSII+CGM (1 RCT; n=78); children with T1DM Hypoglycemic (< 70 mg/dl) AUC (SD) **0.23 (0.41)**	**MDI+SMBG** (1 RCT; n=81); children with T1DM Hypoglycemic (< 70 mg/dl) AUC (SD) **0.25 (0.41)**	12 months	Difference in Hypoglycemic (< 70 mg/dl) AUC at follow up	P=0.79
AHRQ 2012 USA HTA	**Rt-CGM** (4RCTs; n=NA); children & adults with T1DM	**SMBG** (4RCTs; n=NA); children & adults with T1DM	All length of follow-up	Meta-analysis **of non-severe hypoglycemia**	-2.11 minutes/day (-5.66 to 1.44

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
[full rpt in Golden 2012]	Non severe hypoglycemia glucose level less than 70 mg/dL	**Non severe hypoglycemia** (glucose level less than 70 mg/dL)		(glucose level less than 70 mg/dL) outcome Mean between group difference	minutes/day).
	Rt-CGM (7 RCTs; n=NA); children & adults with T1DM Severe hypoglycemia	**SMBG** (7 RCTs; n=NA); children & adults with T1DM **Severe hypoglycemia**	All length of follow-up	Meta-analysis of Severe hypoglycemia outcome RR (95% CI)	0.95 (0.53, 1.69)
	SAP (1 RCTs; n=NA); children & adults with T1DM Severe hypoglycemia = 0 events	**SMBG/MDI** (1 RCTs; n=NA); children & adults with T1DM Severe hypoglycemia = 3 events	All length of follow-up	Meta-analysis of Severe hypoglycemia outcome RR (95% CI)	1.2 (0.7, 2.3)
AHRQ 2012 USA HTA [full rpt in Golden 2012]	**SAP** (1 RCTs; n=NA); children & adults with T1DM Severe hypoglycemia = 0 /8	**SMBG/MDI** (1RCTs; n=NA); children & adults with T1DM Severe hypoglycemia = 1/8	All length of follow-up	Meta-analysis of Severe hypoglycemia outcome RR (95% CI)	3.5 (0.4, 304)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Benkhadra 2017 **Systematic review**	**RT-CGM** (4 RCTs; N=706) All ages with T1DM Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl)	**Control group** (4 RCTs; N=706) All ages with T1DM Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl)	NR	Individual patient data (IPD) Meta-analysis Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl) (95% LL, UL); p value	-8.549 (-31.083, 13.985); p= 0.457
	RT-CGM (3 RCTs; N=130) Children ≤ 12 with T1DM Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl)	**Control group** (3 RCTs; N=130) Children ≤ 12 with T1DM Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl)	NR	Individual patient data (IPD) Meta-analysis Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl) (95% LL, UL); p value	-9.366 (-19.898, 1.167); p= 0.081
	RT-CGM (4 RCTs; N=467) Persons > 15 yrs with T1DM Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl)	**Control group** (4 RCTs; N=467) Persons > 15 yrs with T1DM Time spent in hypoglycemia (<3.3 mmol/l; 60 mg/dl)	NR	Individual patient data (IPD) Meta-analysis Time spent in hypoglycemia (<3.3 mmol/l;	-8.095 (-32.615, 16.425); p= 0.518

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				60 mg/dl) (95% LL, UL); p value	
	RT-CGM (3 RCTs; N=351) All ages with T1DM incidence of hypoglycemic events (<3.9 mmol/l; 70 mg/dl)	**Control group** (3 RCTs; N=351) All ages with T1DM incidence of hypoglycemic events (<3.9 mmol/l; 70 mg/dl)	NR	Individual patient data (IPD) Meta-analysis Mean number of hypoglycemic events (<3.9 mmol/l; 70 mg/dl) (95% LL, UL); p value	0.051(-0.314, 0.416); p=0.785
	RT-CGM (2 RCTs; N=27) Children ≤ 12 with T1DM incidence of hypoglycemic events (<3.9 mmol/l; 70 mg/dl)	**Control group** (2 RCTs; N=27) Children ≤ 12 with T1DM incidence of hypoglycemic events (<3.9 mmol/l; 70 mg/dl)	NR	Individual patient data (IPD) Meta-analysis: Mean number of hypoglycemic events (<3.9 mmol/l; 70 mg/dl) (95% LL, UL); p value	0.392 (0.070 ,0.854); p=0.097
	RT-CGM (3 RCTs; N=277)	**Control group** (2 RCTs; N=277)	NR	Individual patient data	-0.074 (-0.517 ,0.368);

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Persons > 15 yrs with T1DM incidence of hypoglycemic events (<3.9 mmol/l; 70 mg/dl)	Persons > 15 yrs with T1DM incidence of hypoglycemic events (<3.9 mmol/l; 70 mg/dl)		(IPD) Meta-analysis: Mean number of hypoglycemic events (<3.9 mmol/l; 70 mg/dl) (95% LL, UL); p value	p=0.742
Langendam 2012 **Cochrane Library Systematic review**	**RT-CGM** (5 RCTs; n=689) Patients with T1DM **Severe Hypoglycemia**	**SMBG** (5 RCTs; n=689) Patients with T1DM **Severe Hypoglycemia**	6 months	Direct meta-analysis Relative Risk (95% CI) of **Severe Hypoglycemia**; p value	-0.85 (0.32 to 2.26)
	Retrospective-CGM (4 RCTs; n=1/55) Children with T1DM	**SMBG** (4 RCTs; n=1/45) Children with T1DM	3 months	Direct meta-analysis Risk ratio (95% CI) of Severe Hypoglycemia	1.08 [0.07, 15.50]
	Retrospective-CGM (1 RCT; n=18) Children with T1DM Minor hypoglycemic	**SMBG** (1 RCT; n=9) Children with T1DM Minor hypoglycemic	3 months	Fixed Effects meta-analysis of Minor Hypoglycemia outcome	0.53 [-0.68, 1.74]

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Mean(SD)[Episodes] = 1.2 (2.2)	Mean(SD)[Episodes] = 0.67 (1)		Mean difference (95% CI)	
	Retrospective-CGM (1 RCT; n=18) Children with T1DM CGM-derived hypoglycemic Mean(SD)[AUC] = 2061 (1778)	**SMBG** (1 RCT; n=9) Children with T1DM CGM-derived hypoglycemic Mean(SD)[AUC] = 1415 (1256)	3 months	Fixed Effects meta-analysis of CGM-derived hypoglycemic (AUC) Mean difference (95% CI)	646.00 [-515.03, 1807.03]
Langendam 2012 **Cochrane Library Systematic review**	**Real-time CGM** (1 RCT; n=56) Children with T1DM Severe Hypoglycemia = 5/56	**SMBG** (1 RCT; n=58) Children with T1DM Severe Hypoglycemia = 7/58	6 months	Fixed effects direct meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	0.74 [0.25, 2.19]
	Real-time CGM (2 RCTs; n=154) Children with T1DM Severe Hypoglycemia (results not pooled) = 4/78 (study 1) = 0/76 (study 2)	**SMBG** (1 RCT; n=159) Children with T1DM Severe Hypoglycemia (results not pooled) = 4/81 (study 1) = 0/78(study 2)	12 months	Fixed effects direct meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	1.04 [0.27, 4.01] (study 1) 0.11 [0.01, 2.08] (study 2)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Real-time -CGM (1 RCT; n=78) Children with T1DM CGM-derived hypoglycemic Mean(SD)[AUC] = 0.26 (0.4)	**SMBG** (1 RCT; n=81) Children with T1DM CGM-derived hypoglycemic Mean(SD)[AUC] = 0.23 (0.44)	12 months	Random Effects meta-analysis of CGM-derived hypoglycemic (AUC) Mean difference (95% CI)	0.03 [-0.10, 0.16]
	Real-time CGM (1 RCT; n=57) Adolescents with T1DM Severe Hypoglycemia = 3/57	**SMBG** (1 RCT; n=53) Adolescents with T1DM Severe Hypoglycemia = 5/53	6 months	Meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	0.56 [0.14, 2.22]
	Retrospective CGM (1 RCT; n=51) Adults with T1DM Severe Hypoglycemia = 1/51	**SMBG** (1 RCT; n=58) Adults with T1DM Severe Hypoglycemia = 1/58	3 months	Meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	1.14 [0.07, 17.72]
	Retrospective-CGM (1 RCT; n=51) Adults with T1DM CGM-derived hypoglycemic	**SMBG** (1 RCT; n=58) Adults with T1DM CGM-derived hypoglycemic Mean(SD)[	3 months	Fixed Effects meta-analysis of CGM-derived hypoglycemic (Events/day) Mean	-0.30 [-0.73, 0.13]

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Mean(SD)[Events/day] = 1.4 (1.1)	Events/day] = 1.7 (1.2)		difference (95% CI)	
	Real-time CGM (1 RCT; n=14) Adults with T1DM Severe Hypoglycemia = 0/14	**SMBG** (1 RCT; n=13) Adults with T1DM Severe Hypoglycemia = 3/13	3 months	Fixed effects meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	0.13 [0.01, 2.36]
	Real-time CGM (2 RCTs; n=95) Adults with T1DM Severe Hypoglycemia (results not pooled) = 4/43 (study 1) = 5/52 (study 2)	**SMBG** (2 RCTs; n=81) Adults with T1DM Severe Hypoglycemia (results not pooled) = 1/35 (study 1) = 4/46 (study 2)	6 months	Fixed effects meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	[0.38, 27.82] (study 1) 1.11 [0.32, 3.87] (study 2)
	Real-time CGM (1 RCT; n=169) Adults with T1DM Severe Hypoglycemia = 17/169	**SMBG** (1 RCT; n=167) Adults with T1DM Severe Hypoglycemia = 13/167	12 months	Fixed effects meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	1.29 [0.65, 2.58]
	Real-time -CGM (1 RCT; n=40) Adults with T1DM CGM-derived hypoglycemia	**SMBG** (1 RCT; n=31) Adults with T1DM CGM-derived hypoglycemia Mean(SD)[	6 months	Random Effects meta-analysis of CGM-derived hypoglycemia [% time] Mean	-16.60 [-25.06, -8.14]

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Mean(SD)[% time] = 21.6 (12.2)	% time] = 38.2 (21.5)		difference (95% CI)	
	Real-time -CGM (1 RCT; n=169) Adults with T1DM CGM-derived hypoglycemia Mean(SD)[AUC] = 0.25 (0.44)	**SMBG** (1 RCT; n=167) Adults with T1DM CGM-derived hypoglycemia Mean(SD)[AUC] = 0.29 (0.55)	12 months	Random Effects meta-analysis of CGM-derived hypoglycemia (AUC) Mean difference (95% CI)	-0.04 [-0.15, 0.07]
	Real-time CGM (1 RCT; n=54) All ages with T1DM Severe Hypoglycemia = 1/54	**SMBG** (1 RCT; n=54) All ages with T1DM Severe Hypoglycemia = 0/54	3 months	Fixed effects meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	3.00 [0.12, 72.05]
	Real-time CGM (3 RCTs; n=179) All ages with T1DM Severe Hypoglycemia (no pooled results)	**SMBG** (3 RCTs; n=188) All ages with T1DM Severe Hypoglycemia (no pooled results)	6 months	Fixed effects meta-analysis of Severe Hypoglycemia: Risk ratio (95% CI)	2.91 [0.81, 10.51] (study 1) 0.93 [0.34, 2.49] (study 2) 3.51 [0.15, 84.15] (study 3)
	Real-time -CGM (1 RCT; n=54) All ages with T1DM	**SMBG** (1 RCT; n=54) All ages with T1DM	3 months	Fixed Effects meta-analysis of CGM-derived hypoglycemia	0.04 [-0.28, 0.36]

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	CGM-derived hypoglycemia Mean(SD)[Episodes] = -0.13 (0.76)	CGM-derived hypoglycemia Mean(SD)[Episodes] = -0.17 (0.92)		[Episodes] Mean difference (95% CI)	
	Real-time –Intermittent CGM (1 RCT; n=54) All ages with T1DM CGM-derived hypoglycemia Mean(SD)[Episodes] = 0.07 (1.03)	**SMBG** (1 RCT; n=54) All ages with T1DM CGM-derived hypoglycemia Mean(SD)[Episodes] = -0.17 (0.92)	3 months	Fixed Effects meta-analysis of CGM-derived hypoglycemia [Episodes] Mean difference (95% CI)	0.24 [-0.13, 0.61]
	Real-time –CGM (1 RCT; n=112) All ages with T1DM CGM-derived hypoglycemia Mean(SD)[Episodes] 0.045 (0.741) (study 1) 0.1 (0.9) (study 2)	**SMBG** (1 RCT; n=126) All ages with T1DM CGM-derived hypoglycemia Mean(SD)[Episodes] 0.33 (0.736) (study 1) 0.1 (0.7) (study 2)	6 months	Fixed Effects meta-analysis of CGM-derived hypoglycemia [Episodes] Mean difference (95% CI)	-0.29 [-0.53, -0.04] (study 1) 0.0 [-0.32, 0.32] (study 2)
	Real-time –CGM (1 RCT; n=26) All ages with T1DM CGM-derived	**SMBG** (1 RCT; n=29) All ages with T1DM CGM-derived	NR	Fixed Effects meta-analysis of CGM-derived hypoglycemia [% time]	1.10 [-2.87, 5.07]

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	hypoglycemia Mean(SD)[% time] -0.1 (7.69)	hypoglycemia Mean(SD)[% time] -1.2 (7.28)		Mean difference (95% CI)	
	Real-time –CGM (1 RCT; n=66) All ages with T1DM CGM-derived hypoglycemia Mean(SD)[AUC] -0.07 (1.14)	**SMBG** (1 RCT; n=72) All ages with T1DM CGM-derived hypoglycemia Mean(SD) [AUC] 0.31 (1.11)	6 months	Fixed Effects meta-analysis of CGM-derived hypoglycemia [AUC] Mean difference (95% CI)	-0.38 [-0.76, 0.00]
	Real-time –CGM (1 RCT; n=62) All ages with T1DM CGM-derived hypoglycemia Mean(SD)[hours/day] 0.48 (0.57)	**SMBG** (1 RCT; n=58) All ages with T1DM CGM-derived hypoglycemia Mean(SD)[hours/day] 0.97 (1.55)	6 months	Fixed Effects meta-analysis of CGM-derived hypoglycemia [hours/day] Mean difference (95% CI)	-0.49 [-0.91, -0.07]
	CGM augmented pump therapy (1 RCT; n=43) All ages with T1DM Severe hypoglycemia = 4/43	**SMBG** (1 RCT; n=35) All ages with T1DM Severe hypoglycemia = 1/35	6 months	Fixed Effects meta-analysis of severe hypoglycemia: Risk Ratio (95% CI)	3.26 [0.38, 27.82]
	CGM augmented pump	**SMBG**	12 months	Fixed Effects	1.24 [0.67,

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	therapy (1 RCT; n=247) All ages with T1DM Severe hypoglycemia = 21/247	(1 RCT; n=248) All ages with T1DM Severe hypoglycemia = 17/248		meta-analysis of severe hypoglycemia: Risk Ratio (95% CI)	2.29]
	CGM (6 RCTs; n=344) All ages with T1DM Severe hypoglycemia = 29/344	**SMBG** (6 RCTs; n=345) All ages with T1DM Severe hypoglycemia = 26/345	6 months	Random Effects meta-analysis of severe hypoglycemia: Risk Ratio (95% CI): p value	1.05 [0.63, 1.77]; P=0.84 Heterogeneity: (P = 0.51); I^2 =0.0%
	CGM (1 RCT; n=76) All ages with T1DM Severe hypoglycemia = 0/76	**SMBG** (1 RCT; n=78) All ages with T1DM Severe hypoglycemia = 4/78	12 months	Random Effects meta-analysis of severe hypoglycemia: Risk Ratio (95% CI); p value	0.11 [0.01, 2.08]; p=0.14
Floyd 2012 **Systematic review**	**CGM** (no details on meta-analysis inclusions) Hypoglycemic events (episodes/day BG ≤ 70 mg/dl): mean value	**SMBG** (no details on meta-analysis inclusions) Hypoglycemic events (episodes/day BG ≤ 70 mg/dl): mean value	All follow-up times	Random Effects meta-analysis of Hypoglycemic events: Weighted mean difference (95% CI);	0.01 [-0.21,0.23]; p=0.1

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	0.52 ± 0.52	0.52 ± 0.63		p value	
	CGM (no details on meta-analysis inclusions) Duration of hypoglycemia (min/ day BG ≤ 80 mg/dl): mean value 75.34 ± 39.21	**SMBG** (no details on meta-analysis inclusions) Duration of hypoglycemia (min/ day BG ≤ 80 mg/dl): mean value 89.53 ± 19.22	All follow-up times	Random Effects meta-analysis of duration of hypoglycemia: Weighted mean difference (95% CI); p value	-15.2 [-20.3, -10.1]; p<0.0001
	CGM (no details on meta-analysis inclusions) Duration of profound hypoglycemia (min/ day BG ≤55 mg/d):mean value 27.65 ± 31.10	**SMBG** (no details on meta-analysis inclusions) Duration of profound hypoglycemia (min/ day BG ≤55 mg/d):mean value 30.63 ± 14.09	All follow-up times	Random Effects meta-analysis of Duration of profound hypoglycemia: Weighted mean difference (95% CI); p value	-8.8 [-11.8, -5.7]; P<0.0001
Szypowska 2012 **Systematic review**	**RT-CGM** (6 RCTs; n=864) All ages with T1DM Major hypoglycemic episodes	**SMBG** (6 RCTs; n=864) All ages with T1DM Major hypoglycemic episodes	3 to 12 months	Fixed Effects meta-analysis of Major hypoglycemic episodes: Relative risk (95% CI); p value	0.685 (0.412, 1.140); p=0.15 heterogeneity I^2=0%.
Pickup 2011	**CGM** (6 RCTs)	**SMBG** (6 RCTs)	13 to 26 weeks	Two-step IPD meta-analysis	-0.276 (-0.463, -0.089); p=0.004

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Systematic review	All ages with T1DM Hypoglycemia (AUC)	All ages with T1DM Hypoglycemia (AUC)		(fixed effects model) of Hypoglycemia (AUC) WMD (95% CI); p value	Heterogeneity I^2=71.2%
Ghandi 2011 **Systematic review**	**CGM** (4 RCTs; n=381) All ages with T1DM or T2DM Incidence of hypoglycemia (based on number of patients suffering at least one episode of hypoglycemia as the unit of analysis)	**SMBG** (4 RCTs; n=278) All ages with T1DM or T2DM Incidence of hypoglycemia (based on number of patients suffering at least one episode of hypoglycemia as the unit of analysis)	All follow-up times	Direct meta-analysis of hypoglycemia incidence (number of patients): relative risk (95% CI)	1.02 (0.30, 3.45)
	CGM (2 RCTs) All ages with T1DM or T2DM Incidence of hypoglycemia (number of episodes) = 13/720	**SMBG** (2 RCTs) All ages with T1DM or T2DM Incidence of hypoglycemia (number of episodes) = 4/594	All follow-up times	Direct meta-analysis of hypoglycemia incidence (number of episodes): rate ratio (95% CI)	3.50 (1.07, 11.44)
	CGM (2 RCTs)	**SMBG** (2 RCTs)	All follow-up times	Direct meta-analysis of	1.60 (0.24, 10.88)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	All ages with T1DM or T2DM Incidence of nocturnal hypoglycemia (number of episodes) = 130/19566	All ages with T1DM or T2DM Incidence of nocturnal hypoglycemia (number of episodes) = NR		nocturnal hypoglycemia incidence (number of episodes): rate ratio (95% CI)	
Wojciechowski 2011 **Systematic review**	**CGM** (4 RCTs; n=213) All ages with T1DM Frequency of hypoglycemic episodes	**SMBG** (4 RCTs; n=197) All ages with T1DM Frequency of hypoglycemic episodes	≥12 weeks	Fixed effects meta-analysis of hypoglycemia frequency : weighted mean difference (95% CI)	–0.32 [–0.52; –0.13]; p=0.0013 Heterogeneity: (P = 0.4834) I^2 = 0.00%

The AUC is the product of the magnitude and duration of the sensor measured glucose level above or below a specified cut-off level. Higher values for this calculation indicate more numerous, severe or protracted glycemic events.

Table 9 OUTCOME #4: Ketoacidotic events

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Riemsma, 2016 **Prepared for**	**Integrated CSII+CGM (SAP)** (3 RCTs); adults with T1DM Diabetic ketoacidosis (DKA)	**CSII +SMBG** (3 RCTs); adults with T1DM Diabetic ketoacidosis (DKA)	3 months	Indirect meta-analysis of DKA: Relative risk (RR) (95% CI)	0.26 (0.01 to 8.53)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
NICE HTA UK	**Integrated CSII+CGM (SAP)** (3 RCTs); adults with T1DM Diabetic ketoacidosis (DKA)	**MDI +SMBG** (3 RCTs); adults with T1DM Diabetic ketoacidosis (DKA)	3 months	Indirect meta-analysis of DKA: Relative risk (RR) (95% CI)	0.32 (0.04 to 2.86)
	Integrated CSII+CGM (SAP) (1 RCT; n=169); adults with T1DM Patients with diabetic ketoacidosis (DKA) at follow-up = 2/169	**MDI +SMBG** (1 RCT; n=169); adults with T1DM Patients with Diabetic ketoacidosis (DKA) at follow-up = 0/167	12 months	Difference at follow-up	NS
	Integrated CSII+CGM (SAP) (1 RCT; n=78); Children with T1DM Patients with diabetic ketoacidosis (DKA) at follow-up = 1/78	**MDI +SMBG** (1 RCT; n=81); Children with T1DM Patients with Diabetic ketoacidosis (DKA) at follow-up = 1/81	12 months	Difference at follow-up	NS
Langendam 2012 Cochrane Library Systematic review	**Retrospective CGM** (1 RCT; n=18); Children with T1DM ketoacidosis (DKA) at follow-up = 0/18	**SMBG** (1 RCT; n=9); Children with T1DM ketoacidosis (DKA) at follow-up = 0/9	3 months	Fixed effects meta-analysis of DKA: Risk Ratio (95% CI)	No events
	Retrospective CGM (1 RCT; n=19); Children	**SMBG** (1 RCT; n=17); Children	6 months	Fixed effects meta-analysis	2.70 [0.12, 62.17]

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	with T1DM ketoacidosis (DKA) at follow-up = 1/19	with T1DM ketoacidosis (DKA) at follow-up = 0/17		of DKA: Risk Ratio (95% CI)	
	Real time CGM (1 RCT; n=56); Children with T1DM ketoacidosis (DKA) at follow-up = 0/56	**SMBG** (1 RCT; n=58); Children with T1DM ketoacidosis (DKA) at follow-up = 0/58	6 months	Fixed effects meta-analysis of DKA: Risk Ratio (95% CI)	No events
	Real time CGM (1 RCT; n=78); Children with T1DM ketoacidosis (DKA) at follow-up = 1/78	**SMBG** (1 RCT; n=81); Children with T1DM ketoacidosis (DKA) at follow-up = 2/81	12 months	Fixed effects meta-analysis of DKA: Risk Ratio (95% CI)	0.52 [0.05, 5.61]
	Real time CGM (1 RCT; n=57); Adolescents with T1DM ketoacidosis (DKA) at follow-up = 0/57	**SMBG** (1 RCT; n=53); Adolescents with T1DM ketoacidosis (DKA) at follow-up = 1/53	6 months	Fixed effects meta-analysis of DKA: Risk Ratio (95% CI)	0.31 [0.01, 7.46]
	Real time CGM (1 RCT; n=14); adults with T1DM ketoacidosis (DKA) at	**SMBG** (1 RCT; n=13); adults with T1DM ketoacidosis (DKA) at	3 months	Fixed effects meta-analysis of DKA: Risk Ratio (95% CI)	0.31 [0.01, 7.02]

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	follow-up = 0/14	follow-up = 1/13			
	CGM augmented pump therapy (1 RCT; n=43); all ages with T1DM ketoacidosis (DKA) at follow-up = 1/43	**SMBG** (1 RCT; n=35); all ages with T1DM ketoacidosis (DKA) at follow-up = 0/35	6 months	Fixed effects meta-analysis of DKA: Risk Ratio (95% CI)	2.45 [0.10, 58.45]
	Real time CGM (6 RCTs; n=344); all ages with T1DM ketoacidosis (DKA) at follow-up = 7/344	**SMBG** (6 RCTs; n=345); all ages with T1DM ketoacidosis (DKA) at follow-up = 8/345	6 months	Random effects meta-analysis of DKA: Risk Ratio (95% CI)	0.85 [0.32, 2.26]; p=0.75 Heterogeneity (P = 0.66); I2 =0.0%
Wojciechowski 2011 **Systematic review**	**CGM** (4 RCTs; n=NA); all ages with T1DM ketoacidosis (DKA) at follow-up = 1%	**SMBG** (4 RCTs; n=NA); all ages with T1DM ketoacidosis (DKA) at follow-up = 0.3%	>12 weeks	Meta-analysis: Risk Ratio (95% CI)	1.58 [0.38; 6.54]

Table 10 OUTCOME #5: Health Related Quality of Life (*including, all validated HRQoL questionnaires)*

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Riemsma, 2016 **Prepared for NICE HTA UK**	**Integrated CSII+CGM** (1 RCT; n=41) adults T1DM QoL: SF-36 Health Survey measuring general health, mean score (SD)at follow-up = **67.7 (21.6)**	**MDI + SMBG** (1 RCT; n=36) adults T1DM QoL: SF-36 Health Survey measuring general health, mean score (SD) at follow-up = **63.1 (19.1)**	6 months	Direct meta-analysis Difference at follow-up in SF-36 (95% CI) , p value	7.9, (0.5 to 15.3); p = 0.04
	Integrated CSII+CGM (1 RCT; n=169) adults T1DM QoL: SF-36 Health Survey measuring general health, change (SD)at follow-up = **+2.7 (8.07)**	**MDI + SMBG** (1 RCT; n=167) adults T1DM QoL: SF-36 Health Survey measuring general health, change (SD) at follow-up= **–0.3 (7.13)**	12 months	Direct meta-analysis Difference at follow-up in SF-36 (95% CI) , p value	3 (1.36 to 4.64) (SD 7.75),
	Integrated CSII +CGM (N=4 RCTs); adults T1DM DTSQ, Diabetic Treatment Satisfaction Questionnaire	**CSII (pump)+SMBG** (N=4 RCTs); adults T1DM DTSQ, Diabetic Treatment Satisfaction Questionnaire	6 months	Indirect meta-analysis Weighted Mean Difference (WMD) of DTSQ (95% CI)	5.90 (2.22 to 9.58)
	Integrated CSII +CGM (N=2 RCTs); adults T1DM	**MDI + SMBG** (N=2 RCTs); adults T1DM	6 months	Indirect meta-analysis	8.60 (6.28 to 10.92)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	DTSQ, Diabetic Treatment Satisfaction Questionnaire	DTSQ, Diabetic Treatment Satisfaction Questionnaire		Weighted Mean Difference (WMD) of DTSQ (95% CI)	
	MiniMed Veo system (SAP) (1 RCT; n=46); mixed population with T1DM HUS, Hypoglycemia Unawareness Score = **4.7 (95% CI 4.0 to 5.1)**	**CSII+SMBG** (1 RCT; n=49); mixed population with T1DM HUS, Hypoglycemia Unawareness Score at follow-up = **5.1 (95% CI 4.5 to 5.6)**	6 months	Direct meta-analysis Difference at follow-up in HUS (95% CI) , p value	–0.2 (–0.9 to 0.5); p = 0.58
	Integrated CSII+CGM (1 RCT; n=78); children with T1DM PedsQL[a] – psychosocial, change in mean score at follow-up = **3.39**	**MDI+SMBG** (1 RCT; n=81); children with T1DM PedsQL[a] – psychosocial, change in mean score at follow-up = **3.69**	12 months	Direct meta-analysis Difference at follow-up in PedsQL – psychosocial	NS
	Integrated CSII+CGM (1 RCT; n=78); children with T1DM PedsQL[a] – physical, change in mean score at follow-up = **2.53**	**MDI+SMBG** (1 RCT; n=81); children with T1DM PedsQL[a] – physical, change in mean score at follow-up = **1.41**	12 months	Direct meta-analysis Difference at follow-up in PedsQL-physical	NS

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	Integrated CSII+CGM (1 RCT; n=78); children with T1DM HFS[b] – worry, change in mean score at follow-up = **–3.62**	**MDI+SMBG** (1 RCT; n=81); children with T1DM HFS[b] – worry, change in mean score at follow-up = **–2.43**	12 months	Direct meta-analysis Difference at follow-up in HFS - worry	NS
	Integrated CSII+CGM (1 RCT; n=78); children with T1DM HFS[b] – avoidance, change in mean score at follow-up = **–4.01**	**MDI+SMBG** (1 RCT; n=81); children with T1DM HFS[b] – avoidance, change in mean score at follow-up = **–2.25**	12 months	Direct meta-analysis Difference at follow-up in HFS - avoidance	NS
AHRQ 2012 HTA	**SAP** (1 RCT) World Health Organization Well Being Index-5 mother's well-being score (WHO-5)	**SMBG+ CSII (pump)** (1 RCT) Mothers' wellbeing (WHO-5)	12 months	Mean group difference in Mothers' wellbeing (WHO-5) score at follow-up (95% CI)	-2.7 (-14.2 to 8.8)
	Rt-CGM (1 RCT) children with T1DM SF-12 – physical component score	**SMBG** (1 RCT) children with T1DM SF-12 – physical component score	26 weeks	Mean between group difference in SF-12- physical component score at follow-	1.4 (-1.5 to 4.3)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				up (95% CI)	
	Rt-CGM (1 RCT) children with T1DM SF-12 – mental component score	**SMBG** (1 RCT) children with T1DM SF-12 – mental component score	26 weeks	Mean between group difference in SF-12- mental component score at follow-up (95% CI)	-1.6 (-5.9 to 2.7)
	Rt-CGM (1 RCT) children with T1DM PAID - component score	**SMBG** (1 RCT) children with T1DM PAID - component score	26 weeks	Mean between group difference in PAID component score at follow-up (95% CI)	-0.9 (-7.9 to 6.1)
	Rt-CGM (1 RCT) children with T1DM Diabetes Qol Score	**SMBG** (1 RCT) children with T1DM Diabetes Qol Score	26 weeks	Mean between group difference in Diabetes Qol score at follow-up (95% CI)	-3.0 (-6.6 to 0.6)
	Rt-CGM (1 RCT) children with T1DM Hypoglycemia Fear survey (HFS)	**SMBG** (1 RCT) children with T1DM Hypoglycemia Fear survey (HFS	26 weeks	Mean between group difference in HFS score at follow-up (95% CI)	-2.3 (-8.2 to 3.6)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Langendam (2012) Cochrane systematic review	**Real-time CGM** (2 RCTs; n=196); Children with T1DM parents' wellbeing assessed with the WHO-5 questionnaire	**SMBG** (2 RCTs; n=184); Children with T1DM parents' wellbeing assessed with the WHO-5 questionnaire	6 months	Random effects meta-analysis of Standard mean difference (95% CI); p value in parents well-being	0.08 [-0.12, 0.28]; p=0.43 Heterogeneity (P = 0.40); I^2 =0.0%
	Real-time CGM (1 RCT; n=76); Children with T1DM parents' wellbeing assessed with the WHO-5 questionnaire	**SMBG** (1 RCT; n=78); Children with T1DM parents' wellbeing assessed with the WHO-5 questionnaire	12 months	Random effects meta-analysis of Standard mean difference (95% CI); p value in parents wellbeing	0.10 [-0.22, 0.42]; p=0.54
	Real-time CGM (3 RCTs; n=272); Children with T1DM parents' wellbeing assessed with the WHO-5 questionnaire	**SMBG** (3 RCTs; n=262); Children with T1DM parents' wellbeing assessed with the WHO-5 questionnaire	All follow-up lengths	Random effects meta-analysis of Standard mean difference(95% CI); p value in parents well-being	0.09 [-0.08, 0.26] p=0.32 Heterogeneity (P = 0.93); I2 =0.0%
	Real-time CGM (1 RCT; n=42); Adults with T1DM SF-36 - Physical functioning - mean (SD)	**SMBG** (1 RCT; n=33); adults with T1DM SF-36 - Physical functioning - mean (SD)	6 months	Fixed effects meta-analysis of Standard mean difference (95% CI) in SF-36 - Physical	0.11 [-0.35, 0.56] Favors CGM; NS

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	at follow-up = **92.7 (11.2)**	at follow-up = **91.4 (12.7)**		functioning	
	Real-time CGM (1 RCT; n=120); Adults with T1DM SF-36 - Physical functioning - mean (SD) at follow-up = **55.5 (4.9)**	**SMBG** (1 RCT; n=106); adults with T1DM SF-36 - Physical functioning - mean (SD) at follow-up = **54.1 (6.9)**	6 months	Fixed effects meta-analysis of Standard mean difference (95% CI) in SF-36 - Physical functioning	0.24 [-0.03, 0.50] Favors CGM; NS
	Real-time CGM (1 RCT; n=42); Adults with T1DM SF-36 – Mental Health - mean (SD) at follow-up = **79.2 (12.5)**	**SMBG** (1 RCT; n=33); adults with T1DM SF-36 – Mental Health - mean (SD) at follow-up = **76.8 (16.5)**	6 months	Fixed effects meta-analysis of Standard mean difference (95% CI) in SF-36 – Mental Health	0.17 [-0.29, 0.62] Favors CGM; NS
	Real-time CGM (1 RCT; n=120); Adults with T1DM SF-36 – Mental Health - mean (SD) at follow-up **= 48.4 (10.1)**	**SMBG** (1 RCT; n=106); adults with T1DM SF-36 – Mental Health - mean (SD) at follow-up = **48.7 (9.6)**	6 months	Fixed effects meta-analysis of Standard mean difference (95% CI) in SF-36 – Mental Health	-0.03 [-0.29, 0.23] Favors SMBG; NS
	CGM augmented pump therapy (1 RCT; n=42); Adults with T1DM	**SMBG** (1 RCT; n=33); adults with T1DM SF-36 - Physical	6 months	Fixed effects meta-analysis of mean difference (95% CI) in SF-36 - Physical	1.30 [-4.20, 6.80] Favors SMBG; NS

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	SF-36 - Physical functioning - mean (SD) at follow-up = **92.7 (11.2)**	functioning - mean (SD) at follow-up = **91.4 (12.7)**		functioning	
	Real-time CGM (1 RCT; n=42); Adults with T1DM SF-36 – Mental Health - mean (SD) at follow-up = **79.2 (12.5)**	**SMBG** (1 RCT; n=33); adults with T1DM SF-36 – Mental Health - mean (SD) at follow-up = **76.8 (16.5)**	6 months	Fixed effects meta-analysis of mean difference (95% CI) in SF-36 – Mental Health	2.40 [-4.38, 9.18] Favors SMBG; NS
RCTs of Medtronic CGM therapy					
Kordonouri 2010 [ONSET Study] **Europe**	**SAP (Paradigm REAL-Time Insulin Pump and CGM, Medtronic)** RCT; n = 76 Mothers' wellbeing (WHO-5) – mean ± SD Baseline: 49.3±23.9 6 months: 60.2±22.6 12 months: 62.7±18.9 p value for baseline data vs data at 12 months = <0.001	**Pump & SMBG** RCT; n = 78 Mothers' wellbeing (WHO-5) – mean ± SD Baseline: 44.7±21.6 6 months: 60.7±22.6 12 months: 60.8±19.3 p value for baseline data vs data at 12 months = <0.001	Baseline 6 months 12 months	P values of SAP vs Pump for WHO-5 score – mean ± SD at each time frame	Baseline: 0.217 6 months: 0.892 12 months: 0.528
	SAP (Paradigm REAL-Time Insulin Pump and CGM, Medtronic)	**Pump & SMBG** RCT; n = 78	Baseline 6 months 12 months	P values of SAP vs Pump for KIDSCREEN-27:	Baseline: 0.058 6 months:

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	RCT; n = 76 KIDSCREEN-27: Physical wellbeing (children self-report; mean + SD) Baseline: 43.7±9.4 6 months: 49.1±8.5 12 months: 51.2±8.8 p value for baseline data vs data at 12 months = <0.001	KIDSCREEN-27: Physical wellbeing (children self-report; mean + SD) Baseline: 39.8±8.2 6 months: 49.6±9.0 12 months: 49.9±8.2 p value for baseline data vs data at 12 months = <0.001		Physical wellbeing (children self-report; mean + SD) at each time frame	0.685 12 months: 0.359
	SAP (Paradigm REAL-Time Insulin Pump and CGM, Medtronic) RCT; n = 76 KIDSCREEN-27: Psychological wellbeing (children self-report; mean + SD) Baseline: 45.0±10.6 6 months: 49.1±12.7 12 months: 50.4±9.2 p value for baseline data vs data at 12 months = 0.004	**Pump & SMBG** RCT; n = 78 KIDSCREEN-27: Psychological wellbeing (children self-report; mean + SD) Baseline: 44.4±11.0 6 months: 52.3±10.1 12 months: 50.3±10.8 p value for baseline data vs data at 12 months = 0.002	Baseline 6 months 12 months	P values of SAP vs Pump for KIDSCREEN-27: Psychological wellbeing (children self-report; mean + SD) at each time frame	Baseline: 0.847 6 months: 0.153 12 months: 0.905

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	SAP (Paradigm REAL-Time Insulin Pump and CGM, Medtronic) RCT; n = 76 KIDSCREEN-27: Autonomy and parents (children self-report; mean + SD) Baseline: 51.1±8.5 6 months: 50.7±10.6 12 months: 52.5±10.0 p value for baseline data vs data at 12 months = 0.400	**Pump & SMBG** RCT; n = 78 KIDSCREEN-27: Autonomy and parents (children self-report; mean + SD) Baseline: 48.8±9.6 6 months: 51.4±11.01 12 months: 50.2±9.9 p value for baseline data vs data at 12 months = 0.411	Baseline 6 months 12 months	P values of SAP vs Pump for KIDSCREEN-27: Autonomy and parents (children self-report; mean + SD) at each time frame	Baseline: 0.313 6 months: 0.648 12 months: 0.158
	SAP (Paradigm REAL-Time Insulin Pump and CGM, Medtronic) RCT; n = 76 KIDSCREEN-27: Social support and peers (children self-report; mean + SD) Baseline: 47.1±11.0 6 months: 53.3±9.2 12 months: 52.4±9.6 p value for baseline data vs data at 12 months =	**Pump & SMBG** RCT; n = 78 KIDSCREEN-27: Social support and peers (children self-report; mean + SD) Baseline: 44.2±10.7 6 months: 50.9±9.6 12 months: 50.8±9.0 p value for baseline data vs data at 12 months = 0.002	Baseline 6 months 12 months	P values of SAP vs Pump for KIDSCREEN-27: Social support and peers (children self-report; mean + SD) at each time frame	Baseline: 0.370 6 months: 0.262 12 months: 0.377

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	0.090				
	SAP (Paradigm REAL-Time Insulin Pump and CGM, Medtronic) RCT; n = 76 KIDSCREEN-27: School environment (children self-report; mean + SD) Baseline: 47.4±11.7 6 months: 49.7±11.7 12 months: 52.8±9.8 p value for baseline data vs data at 12 months = 0.170	**Pump & SMBG** RCT; n = 78 KIDSCREEN-27: School environment (children self-report; mean + SD) Baseline: 45.4±10.1 6 months: 51.3±10.1 12 months: 51.3±10.2 p value for baseline data vs data at 12 months = 0.005	Baseline 6 months 12 months	P values of SAP vs Pump for KIDSCREEN-27: School environment (children self-report; mean + SD) at each time frame	Baseline: 0.612 6 months: 0.493 12 months: 0.436
Newman2009 [MITRE study] UK	**MiniMed CGM (Medtronic)** RCT; n=54; Adults T1DM or T2DM Diabetes-specific quality of life (Mean (SD)) Baseline: 4.4 (2.3) 6 months: 4.7 (1.8) 12 months: 4.9 (1.7) 18 months: 5.0 (1.6)	**Standard control group** RCT; n=51: Adults T1DM or T2DM Diabetes-specific quality of life (Mean (SD)) Baseline: 4.6 (2.2) 6 months: 4.9 (1.9) 12 months: 5.0 (1.8) 18 months: 4.6 (1.7)	Baseline to 6, 12 and 18 months	Results of repeated measures ANOVAs on diabetes specific quality of life Mean Square (p value)	Time: 0.845; p=0.602 Arm: 26.145; p=0.089 TimexArm: 2.074; p=0.093
	MiniMed CGM	**Standard control group**	Baseline to 6,	Results of	Time: 171.488;

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	(Medtronic) RCT; n=54; Adults T1DM or T2DM Hypoglycemia Fear survey (Mean (SD)) Baseline: 18.8 (12.0) 6 months: 18.4 (13.3) 12 months: 16.7 (12.5) 18 months: 16.2 (12.3)	RCT; n=51: Adults T1DM or T2DM Hypoglycemia Fear survey (Mean (SD)) Baseline: 18.4 (13.0) 6 months: 18.0 (13.3) 12 months: 17.3 (10.6) 18 months: 17.6 (11.7)	12 and 18 months	repeated measures ANOVAs on Hypoglycemia Fear survey [c] Mean Square (p value)	p= 0.016 Arm: 877.978; p= 0.171 Time x Arm: 12.008; p= 0.960

a The higher the PedsQL score, the higher the quality of life.
b The higher the HF score, the higher the quality of life.
c ANOVA includes additional treatment arms (Glucowatch and attention control arms)

Table 11 HARM #1: Local adverse effects: (skin irritation, wound infection, sensor site occlusion)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
RCTs of Medtronic CGM therapy					
Hermandies 2011 [Eurythmics trial]	**Paradigm sensor-augmented pump therapy (Medtronic MiniMed)** Skin related problems	**SMBG with MDI** Skin related problems 0/39 (0 %)	26 weeks	Number of patients (%) experiencing skin related adverse events	SAP: 17/44 (38.6%) SMBG: 0/39 (0%)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	17/44 (38.6%) 17 patients reported skin-related problems (itch / exanthema / infection / redness / plaster allergy / bruising / hematoma) at the sensor or insulin infusion site.				
Bergenstal (2010) – STAR 3	**MiniMed CGMS linked with Paradigm pump** cellulitis (related to insertion- site infections) 2/244 (0.8%)	**SMBG with MDI** cellulitis (related to insertion- site infections) 0/241 (0%)	52 weeks	Number of patients (%) experiencing cellulitis	CGM: 2/244 (0.8%) SMBG: 0%
Newman (2009) MITRE Study	**MiniMed CGM (Medtronic)** N=102 Reported a skin reaction, n (%) = 5 (7)	**Glucowatch** N=100 Reported a skin reaction, n (%)=41 (98)	Week number 12	Number reporting a skin reaction, / number wearing device (%)	**MiniMed CGM = 5/72 (7%) Glucowatch** =41/42 (98%)
	MiniMed CGM (Medtronic) N=102 Reported a skin reaction, n (%) = 3 (6)	**Glucowatch** N=100 Reported a skin reaction, n (%)=14 (93)	Week number 78	Number reporting a skin reaction,/ number wearing device (%)	**MiniMed CGM = 3/52 (6%) Glucowatch** =14/15 (93%)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	MiniMed CGM (Medtronic) N=102	**Glucowatch** N=100	Week number 12	Duration of skin problems (days), median (IQR)	**MiniMed CGM** = 3 (2–4) **Glucowatch** =13 (5–28)
	MiniMed CGM (Medtronic) N=102	**Glucowatch** N=100	Week number 12	Removed monitor because of skin problem, n (%)	**MiniMed CGM** = 0 **Glucowatch** = 8 (20)
	MiniMed CGM (Medtronic) N=102	**Glucowatch** N=100	Week number 12	MITRE skin scale score of typical skin reaction, median (IQR)a	**MiniMed CGM** = 0 (0–3) **Glucowatch** = 4 (2–5)
	MiniMed CGM (Medtronic) N=102	**Glucowatch** N=100	Week number 12	Severe reaction (≥ 6) on the MITRE skin scale n (%)	**MiniMed CGM** = 0 **Glucowatch** = 11 (27)

Table 12 HARM #2: Serious adverse events

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
RCTs of Medtronic CGM therapy					
Hermandies 2011 [**Eurythmics trial**]	Paradigm sensor-augmented pump therapy (Medtronic MiniMed) Serious adverse events (all) 2/44 (4.5%)	SMBG Serious adverse events (all) 5/39 (12.8%)	26 weeks	Number (%) experiencing serious AE (any reason) in each treatment arm	2/44 (4.5%) in the SAP arm 5/39 (12.8%) in SMBG group
	Paradigm sensor-augmented pump therapy (Medtronic MiniMed) Serious adverse events (device related) 1/44 (2.3%)	SMBG Serious adverse events (device related) 0/39 (0%)	26 weeks	Number (%) experiencing serious AE (device-related reason) in each treatment arm	1 (2.3%) hospital SAE in the SAP arm for ketoacidosis because of pump failure 0/39 in SMBG arm
Raccah 2009 (**RealTrend Study**)	Paradigm REAL-Time system SAP (Medtronic MiniMed) Serious adverse events (all) =3/55 (5.5%)	CSII & SMBG Serious adverse events (all) =7/60 (11.7%)	26 weeks	Number (%) experiencing serious AE (any reason) in each treatment arm	3/55 (5.5%) in the SAP arm 7/60 (11.7%) in CSII/SMBG group
Battelino (2012) **SWITCH study**	Guardian REAL-Time + insulin pump: SENSOR ON	Guardian REAL-Time + insulin pump: SENSOR OFF	26 weeks	Incidence of severe hypoglycemic events in each	Sensor ON: 5.70 per 100 patient-years (n=4)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
				treatment arm/ per 100 patient years (n)	Sensor OFF: 2.83 per 100 patient-years (n=2)

Table 13 HARM #3: Pain

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Murphy 2008	**CGMS Gold Medtronic** (n=38)	**Standard antenatal care** (n=33)	During pregnancy	Pain	One woman who experienced pain after insertion of the sensor withdrew from the study

Table 14 HARM #4: Mortality (all causes; therapy-related)

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
Langendam (2012) Cochrane systematic review	Death was not measured in any of the included studies in adults, children or adolescents.				
Yeh 2011 Systematic review	None of the studies reported on mortality or any of the process measures.				
RCTs of Medtronic CGM therapy					
Alfadhli 2017 RCT Saudi Arabia	**Guardian® REAL-Time CGM + SMBG** RCT; n= 60; gestational diabetes (GDM) Neonatal death = 3.4%	**SMBG** RCT; n= 62; gestational diabetes (GDM) Neonatal death = 1.6%	3-7 days	Odds ratio (95% CI) for difference in neonatal deaths	2.14 (0.149 to 20.76); p= 0.613
Secher 2013 RCT Denmark	**Guardian RT-CGMS with the Sof-Sensor + routine care** RCT; n=79 Pregnant women with T1 or T2DM Perinatal deaths (miscarriage) for T1DM = 3/63 Perinatal deaths	**Routine care** RCT; n=79 Pregnant women with T1 or T2DM Perinatal deaths (miscarriage) for T1DM = 1/60 Perinatal deaths (miscarriage) for T2DM = 1/15	6 days monitored at 8, 12, 21, 27, and 33 weeks	P value for perinatal deaths	T1DM: p=0.62 T2DM: p=0.48

Citation (Author, Year)	Treatment Group Rate # pts w/outcome in group total # of pts in group	Control Group Rate # pts w/outcome in group total # of pts in group	Time Frame	Statistical Measure	Result
	(miscarriage) for T2DM = 0/16				
Bergenstal (2010) – STAR 3	**MiniMed CGMS linked with Paradigm pump** Patient death 0/244 (0%)	**SMBG with MDI** Death (cause was sudden cardiac arrest in a patient with a history of cardiovascular disease) 1/241 (0.4%)	52 weeks	Number (%) of deaths during the study period	CGM: 0/244 (0%) SMBG: 1/241 (0.4%)

Diagnostic Tables

Please fill out a table for each outcome, as specified on the service review webpage.

Not applicable

OUTCOME #1: _____

Citation (Author, Year)	Baseline prevalence in population being tested	Time frame	Statistical Measure	Result

Appendix A: Abbreviations and Acronyms

AIAQS	Agència d'Informació, Avaluació i Qualitat en Salut
AE	Adverse Event
AHRQ	Agency for Healthcare Research Quality
AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali
CGM	Continuous glucose monitor
CSII	Continuous subcutaneous insulin infusion
DKA	Diabetic Ketoacidosis
GDM	Gestational diabetes mellitus
HTA	Health Technology Assessment
IDDM	Insulin dependent diabetes mellitus
IQWIG	Institute for Quality and Efficiency in Health Care;
IPD	Individual patient data
LGS	Low glucose suspend
LL	Lower limit
MDI	Multiple daily injections
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OHTAC	Ontario Health Technology Advisory Committee
PLGS	Predictive Low glucose suspend
PRO	Patient Reported Outcome
RCT	Randomized controlled trial
RT-CGMS	Real-time continuous glucose monitoring systems
RR	Risk ratio/ relative risk
SAP	Sensor augmented pump
SBU	Swedish Agency for Health Technology Assessment
SMBG	Self-monitoring blood glucose
SR	Systematic review
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UL	Upper limit
WMD	Weighted Mean Difference

Appendix B: Summary of included studies

Table 15 Main characteristics of included Health Technology Assessments for CGM and SAP

HTA Agency (Year) Country	Included studies (N) Patient population	Interventions examined Meta-analysis (Y/N)	Main Conclusions
ECRI (2016) USA	4 studies; IDDM	SAP with Threshold suspend/ LGS ; (N)	SAP with LGS may reduce the severity and duration of hypoglycemia.
NIHR/NICE (2016) UK	19 studies; T1DM in adults and children	CSII + CGMS vs CSII & SMBG; (Y*)	Positive recommendation for funding of CGM models (MiniMed Paradigm Veo)
IQWIG (2015) Germany	15 RCTs; IDDM	Rt-CGM vs SMBG/Retro-CGM; (Y)	Rt-CGM has efficacy benefits to select populations with T1DM.
SBU (2013) Sweden	18 studies; T1DM, T2DM & GDM in adults and children;	CGM, SAP vs SMBG/MDI; (NA)	Persons with diabetes are considerably more satisfied with CGM & SAP than with MDI/SMBG.
OHTAC (2011) Canada	2 RCTs; T1DM, T2DM & GDM in adults and children	RT-CGM (+/- CSII)vs SMBG; (Y)	Evidence is of moderate quality but is currently insufficient to make conclusions on effectiveness
AGENAS (2012) Italy	1 SR and 3 RCTs; T1DM aged 0-18yrs	SAP/ CGMS/CSII; (N)	SAP has benefits to select populations with T1DM
AHRQ (2012); USA	13 studies; patients with DM	Rt-CGM vs SMBG; (Y)	Clinically significant reductions in HbA1c levels achieved with SAP.
AIAQS (2010) Spain (Cataluña)	14 RCTs & 2 B&A studies; T1DM in adults and children	RT-CGM (+/- CSII) vs SMBG; (N)	CGM systems are effective at 6 months in varied diabetic populations

Abbreviations: AIAQS, Agència d'Informació, Avaluació i Qualitat en Salut; AHRQ, Agency for Healthcare Research Quality; AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali; B&A, before and after; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; GDM, gestational diabetes mellitus; IDDM, insulin dependent diabetes mellitus; IQWIG, Institute for Quality and Efficiency in Health Care; LGS, low glucose suspend; NA, not available; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health Research; OHTAC, Ontario Health Technology Advisory Committee; RCT, randomized controlled trials; RT-CGMS, real-time continuous glucose monitoring systems; SAP, sensor augmented pump; SR, systematic review; SBU, SBU Swedish Agency for Health Technology Assessment; SMBG, self-monitoring blood glucose; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus;*Indirect meta-analyses; [a]Results also published in these systematic reviews

Table 16 Main characteristics of included systematic reviews for CGM

1st Author (Year)	Included studies (N) Meta-analysis (Y/N)	Patients (N)	Interventions
Benkhadra (2017)	11 RCTs (Y)*	Adults & children with T1DM (NR)	RT-CGM vs. SMBG
Matsuda (2014)	2 RCTs (Y)	Adolescents T1DM (NR)	CGM vs SMBG
Poolsup (2013)	15 RCTs (Y)	Adults (T2DM; N=161) & children (T1DM; N=817)	CGM vs SMBG
Floyd (2012)	14 RCTs (Y)	Adults & children with T1DM (n=1188)	CGM vs SMBG
Langendam (2012) [Cochrane]	22 RCTs (Y)	Adults & children with T1DM (n=2883)	CGM vs SMBG
Szypowska (2012)	7 RCTs (Y)	Adults & children with T1DM (n=948)	RT-CGM (+/- CSII) vs SMBG
Hoeks (2011)	9 RCTs (N)	Adults & children with T1 or T2DM (NR)	Rt-CGM vs SMBG or retro-CGM
Pickup (2011)	6 RCTs (Y)*	Adults & children with T1DM (N=449)	CGM vs SMBG
Gandhi (2011)	19 RCTs (Y)	Adults & children with T1 or T2DM (n=1801)	CGM vs SMBG
Wojciechowski (2011)	14 RCTs (Y)	Adults & children with T1DM (N=1268)	CGM vs SMBG
Chetty (2008)	7 RCTs (Y)	Adults & children with T1DM (n=335)	CGM vs SMBG
Golicki (2008)	5 RCTs (Y)	Children with T1DM (n=131)	CGM vs SMBG

Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; RCT, randomized controlled trials; retro-CGM, retrospective continuous glucose monitoring; NR, not reported; RT-CGMS, real-time continuous glucose monitoring systems; SMBG, self-monitoring blood glucose; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

* Individual patient data meta-analyses

Table 17 Main characteristics of included published **Randomized Controlled Trials (RCTs)** for CGM/SAP

1st Author [Study name] (Year) Country	Patients	Interventions (N patients)	Mean age % male	Baseline HbA1c	CGM duration of use (weeks)	CGM frequency of use	CGM DEVICES USED
Alfadhli 2016 Saudi Arabia	GDM	rtCGM(68) SMBG (62).	rtCGM: 33 0%	rtCGM:5.6	3–7 days	Daily	Guardian® REAL-Time
Wei 2016 China	GDM	rtCGM(55) SMBG (62)	30 0%	5.7/5.8	Until birth	Daily	Gold Medtronic MiniMed
Buckingham (2015) Canada/US	T1DM two age-cohorts: 11–14 and 3–10 years	MiniMed Vs Control nights (n=81)	13/8 56%/46%	7.7%/7.8%	42 nights	nightly	Paradigm REAL-Time Veo System with Enlite glucose sensor
Bergenstal (2013) **ASPIRE In-Home** USA	T1DM 16 to 69 yrs	SAP with threshold suspend (TS) (n = 121) SAP control (n = 126)	SAP TS: 41.6 SAP TS: 38%	SAP TS:7.3	12	80% of the time	MiniMed Veo Paradigm Revel 2.0 insulin pump and Enlite sensors
Secher 2013 Denmark	Pregnant women with T1 or T2DM	Rt-CGM (79) SMBG (75)	32/31 0%	6.6/6.8	Until birth	6 days	Guardian RT-CGMS with the Sof-Sensor
Battelino [SWITCH] 2012 Europe	Adults, children, T1DM	SAP - On/Off (77) SAP: Off/On (76)	28 On/off-49%	On/off-8.5%	26	unclear	Guardian REAL-Time (Medtronic)
Garg 2012 Aspire in-clinic	Adults/ adolescents T1DM	SAP/LGS-ON (25) SAP/LGS-OFF (25)	34 56%	7.9	2 hrs	In-clinic	Sof-Sensor (Medtronic MiniMed, Inc.)
Bukara 2011 Bosnia	Children T1DM	CGM (40) SMBG (40)	CGM:13.7 CGM:45%	CGM:10.0	26	72 hrs	Medtronic MiniMed
Hermanides 2011 [Eurythmics] Europe	Adults T1DM	SAP (n=44) SMBG (39)	SAP: 39.3 SAP: 50%	SAP: 8.47	26	NA	Paradigm SAP therapy (Medtronic MiniMed
Bergenstal (2010) **[STAR-3]** USA	T1DM Children & adults	SAP with MiniMed Paradigm RT (n= 244) MDI (n= 241)	32.2 57%	8.3	52	Daily	MiniMed Paradigm REAL-Time System, Medtronic
Kordonouri 2010 [ONSET] Europe	Children T1DM	SAP (76) Pump& SMBG (78)	8.8 52%	11.3	52	Daily	Guardian REALTime (Medtronic)
O'Connell, 2009 Australia	Adults, children, T1DM	CGM (31) SMBG (31)	23 29%	7.3% CGM 7.5% control	12	Willingness to use sensor at 70% of the	CGMS Gold (Medtronic)

1st Author [Study name] (Year) Country	Patients	Interventions (N patients)	Mean age % male	Baseline HbA1c	CGM duration of use (weeks)	CGM frequency of use	CGM DEVICES USED
						total study duration	
Newman [MITRE] 2009 UK	Adults T1DM or T2DM	Glucowatch (100) CGMS (102) AC (100) SoC (102)	52 55%	9.0	18 months	unclear	MiniMed CGM (Medtronic)
Raccah, 2009 France	Adults, children, T1DM	CGM (55) SMBG (60)	28 32%	>9%	26	Required to use glucose sensors at least 70% of the time	MiniMed Paradigm REAL-Time system
Hirsch 2008 USA	Adults, children, T1DM	CGM (66) SMBG (72)	33 44%	8.44%	26	Continuous (approx..6 days per week)	Paradigm 722 System
Murphy 2008 UK	Pregnant women T1 or T2DM	CGM (38) SMBG (33)	CGM: 30.2 0%	CGM: 7.2%	4-6 weeks during pregnancy	5-7 days	Gold Medtronic-MiniMed
Yoo 2008 Korea	Adults T2DM	CGM (32) SMBG (33)	55/58 35%/50%	9.1/8.7	12	4x per wk	Guardian RT (Medtronic)

Abbreviations: AC, attention control; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; GDM, gestational diabetes mellitus; LGS, low glucose suspend; MDI, multiple daily injection; RCT, randomized controlled trials; retro-CGM, retrospective continuous glucose monitoring; NR, not reported; RT-CGMS, real-time continuous glucose monitoring systems; SAP, sensor augmented pump; SMBG, self-monitoring blood glucose; SoC, standard of Care; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

*F12 month extension study of the JDRF CGMS study – CGM follow up

**only describes results from the CGM arm

***6 month extension

Appendix C: Quality Appraisal Checklists

Table 18 Quality appraisal checklist for included HTA reports

Description				Section 1: Internal Validity								Section 2: Overall Appraisal			
				1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.1	2.2	2.3	2.4
Citation	Technology	Reviewer	Date	The study addresses an appropriate and clearly focused question.	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	The literature search is sufficiently rigorous to identify all the relevant studies.	The criteria used to select articles for inclusion is appropriate.	Study quality is assessed and taken into account.	There are enough similarities between the studies selected to make combining them reasonable.	Competing interests of members have been recorded and addressed.	Views of funding body have not influenced the content of the study.	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	Are the results of this study directly applicable to the patient group targeted by this key question?	Other reviewer comments:
Riemsma, R et al 2016, Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (CGM] for managing blood glucose levels in type 1 diabetes: A systematic review and economic evaluation: *Health Technology Assessment,* National Institute of Clinical Excellence. Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system). *NICE Clin Guid.* 2016;(February 2016).	CGM & SAP	LS	04/10/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	High quality systematic review with indirect meta-analyses
ECRI Institute. Threshold suspend Insulin Delivery Systems for Managing Hypoglycemia in Patients with Type 1 Diabetes Mellitus. HTA Inf Serv. 2016;(July):1-48	SAP with LGS	LS	04/10/17	YES	YES	YES	YES	YES	NA	YES	YES	GOOD	NA	YES	This is a good quality emerging technology evidence report.

Description				Section 1: Internal Validity								Section 2: Overall Appraisal			
				1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.1	2.2	2.3	2.4
Citation	Technology	Reviewer	Date	The study addresses an appropriate and clearly focused question.	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	The literature search is sufficiently rigorous to identify all the relevant studies.	The criteria used to select articles for inclusion is appropriate.	Study quality is assessed and taken into account.	There are enough similarities between the studies selected to make combining them reasonable.	Competing interests of members have been recorded and addressed.	Views of funding body have not influenced the content of the study.	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	Are the results of this study directly applicable to the patient group targeted by this key question?	Other reviewer comments:
IQWiG Reports. 25 March 2015 Continuous interstitial glucose monitoring (CGM) with real-time measurement devices in insulin-dependent diabetes mellitus [English Executive Summary] – Commission No. D12-01 IQWiG. Continuous interstitial glucose monitoring (CGM) with real-time measurement devices in insulin-dependent diabetes mellitus (FINAL REPORT IN GERMAN). Heal Technol Assess Database. 2015;(3).	CGM	LS	04/26/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	Very good quality SR within a HTA
SBU Alert report no 2013-04 Continuous subcutaneous glucose monitoring for diabetes. *www.sbu.se/201304e* Technology SSC on H. Continuous Subcutaneous Glucose Monitoring for Diabetes [Internet]. SBU Syst Rev Summ. 2013;SBU Alert(october):1-3.	CGM & SAP	LS	04/26/17	YES	YES	YES	YES	YES	NA	YES	YES	GOOD	NA	YES	Good quality HTA
Medical Advisory Secretariat. Continuous glucose monitoring for patients with diabetes: an evidence based analysis. *Ont Health Technol* . 2011 July; 11(4) 1-29.	CGM	LS	04/26/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	Strict inclusion criteria meant only 2 RCTs included for review.

Description				Section 1: Internal Validity								Section 2: Overall Appraisal			
				1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.1	2.2	2.3	2.4
Citation	Technology	Reviewer	Date	The study addresses an appropriate and clearly focused question.	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	The literature search is sufficiently rigorous to identify all the relevant studies.	The criteria used to select articles for inclusion is appropriate.	Study quality is assessed and taken into account.	There are enough similarities between the studies selected to make combining them reasonable.	Competing interests of members have been recorded and addressed.	Views of funding body have not influenced the content of the study.	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	Are the results of this study directly applicable to the patient group targeted by this key question?	Other reviewer comments:
Lo Scalzo A, Lenzi L et al. *HTA report*: new devices for the management of glycaemia in young diabetics, Rome, September 2012.	CGM	LS	04/26/17	YES	YES	YES	YES	YES	NA	YES	YES	GOOD	NA	YES	Only 3 RCTs included.
Golden SH, Brown T, Yeh HC, et al. . Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Comparative Effectiveness Review No. 57. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA-290-2007-10061-I.) ***AHRQ Publication No****. 12-EHC036-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2012.* Golden S, Sapir T. Methods for Insulin Delivery and Glucose Monitoring in Diabetes: Summary of a Comparative Effectiveness Review. J Manag Care Pharm. 2012;18(6):S1-S17. Yeh, H. C., Brown, T. T., et al. 2012, Comparative effectiveness and safety of	CGM	LS	04/26/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	Good quality HTA published in separate papers (with a 2016 update of the literature search).

Description				Section 1: Internal Validity								Section 2: Overall Appraisal			
				1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.1	2.2	2.3	2.4
Citation	Technology	Reviewer	Date	The study addresses an appropriate and clearly focused question.	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	The literature search is sufficiently rigorous to identify all the relevant studies.	The criteria used to select articles for inclusion is appropriate.	Study quality is assessed and taken into account.	There are enough similarities between the studies selected to make combining them reasonable.	Competing interests of members have been recorded and addressed.	Views of funding body have not influenced the content of the study.	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	Are the results of this study directly applicable to the patient group targeted by this key question?	Other reviewer comments:
methods of insulin delivery and glucose monitoring for diabetes mellitus: A systematic review and meta-analysis: *Annals of Internal Medicine,* v. 157, p. 336-347 AHRQ. AHRQ Systematic Review Surveillance Program: CER #57: Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. 2016. https://effectivehealthcare.ahrq.gov/ehc/products/242/2182/insulin-blood-sugar-surveillance-160215.pdf.															
Solans M, Kotzeva A, Almazán A. Sistemas de monitorización continua de glucose en tiempo real. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad, Política Social e Igualdad. Ministerio de Ciencia e Innovación. Agència d'Informació, Avaluació i Qualitat en Salut de Cataluña; 2011. *Informes de Evaluación de Tecnologías Sanitarias, AIAQS* núm. 2010/06.	CGM	LS	04/26/17	YES	YES	YES	YES	YES	NA	NA	NA	GOOD	NA	YES	14 RCTs included; good quality review

Abbreviations: CGM, Continuous glucose monitoring; LGS, low glucose suspend; LS, L Strachan; SAP, Sensor augmented insulin pump; SR, systematic reviews;

Table 19 Quality appraisal checklist for included systematic reviews and meta-analyses

Description				Section 1: Internal Validity								Section 2: Overall Appraisal			
				1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.1	2.2	2.3	2.4
Citation	Technology	Reviewer	Date	The study addresses an appropriate and clearly focused question.	An adequate description of the methodology used is included, and the methods used are appropriate to the	The literature search is sufficiently rigorous to identify all the relevant studies.	The criteria used to select articles for inclusion is appropriate.	Study quality is assessed and taken into account.	There are enough similarities between the studies selected to make combining them reasonable.	Competing interests of members have been recorded and addressed.	Views of funding body have not influenced the content of the study.	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	Are the results of this study directly applicable to the patient group targeted by this key question?	Other reviewer comments:
Benkhadra, K., Alahdab, F, et al., 2017, Real-time continuous glucose monitoring in type 1 diabetes: a systematic review and individual patient data meta-analysis: *Clinical Endocrinology*, v. 86, p. 354-360	CGM	LS	04/20/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	IPD meta-analysis. Reporting quality fair – missing forest plots.
Matsuda, E. and Brennan, P., 2014, The effectiveness of continuous glucose monitoring for type 1 diabetic adolescents using continuous subcutaneous insulin infusion pumps: A systematic review**: *JBI Database of Systematic Reviews and Implementation Reports,*** v. 12, p. 88-120.	CGM	LS	04/20/17	YES	YES	YES	YES	YES	YES	UNCLEAR	UN-CLEAR	GOOD	NA	YES	Small SR with narrow research question. Good quality JBI run SR.
Poolsup, N., Suksomboon, N., et al. 2013, Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes: *Diabetology and Metabolic Syndrome,* v. 5:39	CGM	LS	04/20/17	YES	YES	YES	YES	YES	YES	YES	UN-CLEAR	GOOD	NA	YES	-
Floyd, B., Chandra, P., et al., 2012, Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus: *Journal of Diabetes Science and Technology*, v. 6, p. 1094-1102.	CGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	14 RCTs included; good quality SR
Langendam, M., Luijf, Y. M., et al., 2012, Continuous glucose monitoring systems for type 1 diabetes mellitus: *Cochrane.Database.Syst.Rev,* v. 1, p. CD008101.	CGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	High quality Cochrane SR
Szypowska, A., Ramotowska, A., et al., 2012, Beneficial effect of real-time continuous glucose	rtCGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	7 RCTs included; good quality SR

Description				Section 1: Internal Validity								Section 2: Overall Appraisal			
				1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.1	2.2	2.3	2.4
Citation	Technology	Reviewer	Date	The study addresses an appropriate and clearly focused question.	An adequate description of the methodology used is included, and the methods used are appropriate to the	The literature search is sufficiently rigorous to identify all the relevant studies.	The criteria used to select articles for inclusion is appropriate.	Study quality is assessed and taken into account.	There are enough similarities between the studies selected to make combining them reasonable.	Competing interests of members have been recorded and addressed.	Views of funding body have not influenced the content of the study.	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	Are the results of this study directly applicable to the patient group targeted by this key question?	Other reviewer comments:
monitoring system on glycemic control in type 1 diabetic patients: Systematic review and meta-analysis of randomized trials*: European Journal of Endocrinology,* v. 166, p. 567-574															
Hoeks, L. B., Greven, W. L et al., 2011, Real-time continuous glucose monitoring system for treatment of diabetes: A systematic review: *Diabetic Medicine,* v. 28, p. 386-394.	rtCGM	LS	04/27/17	YES	YES	YES	YES	YES	NO	YES	UN-CLEAR	GOOD	NA	YES	9 RCTs included
Pickup, J. C., Freeman, S. C., and Sutton, A. J., 2011, Glycemic control in type 1 diabetes during real time continuous glucose monitoring compared with self-monitoring of blood glucose: Meta-analysis of randomized controlled trials using individual patient data: *BMJ*, v. 343: d3805	CGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	IPD meta-analysis
Gandhi, G. Y., Kovalaske, M., et al 2011, Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials: *Journal of Diabetes Science and Technology*, v. 5, p. 952-965.	CGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	NO	UN-CLEAR	FAIR	Methods appear robust & as such lack of detail around funding or competing interests is unlikely to impact conclusions	YES	19 RCTs included.
Wojciechowski, P., Rys›, P., et al., 2011, Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in	CGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	YES	UN-CLEAR	GOOD	NA	YES	14 RCTs included; good quality SR

Description				Section 1: Internal Validity								Section 2: Overall Appraisal			
				1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.1	2.2	2.3	2.4
Citation	Technology	Reviewer	Date	The study addresses an appropriate and clearly focused question.	An adequate description of the methodology used is included, and the methods used are appropriate to the	The literature search is sufficiently rigorous to identify all the relevant studies.	The criteria used to select articles for inclusion is appropriate.	Study quality is assessed and taken into account.	There are enough similarities between the studies selected to make combining them reasonable.	Competing interests of members have been recorded and addressed.	Views of funding body have not influenced the content of the study.	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	Are the results of this study directly applicable to the patient group targeted by this key question?	Other reviewer comments:
type 1 diabetes: Systematic review and meta-analysis: *Polskie Archiwum Medycyny Wewnetrznej,* v. 121, p. 333-344.															
Chetty, V. T., Almulla, A., et al., 2008, The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in Type I diabetic patients: A systematic review: *Diabetes Research and Clinical Practice*, v. 81, p. 79-87.	CGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	YES	UN-CLEAR	GOOD	NA	YES	5 RCTs included.
Golicki, D. T., Golicka, D. et al., 2008, Continuous Glucose Monitoring System in children with type 1 diabetes mellitus: a systematic review and meta-analysis: *Diabetologia,* v. 51, p. 233-240.	CGM	LS	04/27/17	YES	YES	YES	YES	YES	YES	YES	YES	GOOD	NA	YES	

Center for Evidence-based Policy 2009. Adapted from NICE and SIGN materials.

Abbreviations: CGM, Continuous glucose monitoring; JBI; Joanna Briggs Institute; LGS, low glucose suspend; LS, L Strachan; rtCGM, real-time Continuous glucose monitoring; SAP, Sensor augmented insulin pump; SR, systematic reviews;

Table 20 Quality appraisal checklist for included Randomized Controlled trials (RCTs from 2016-2013)

Description	Citations				
	Alfadhli 2016	**Wei 2016**	**Buckingham (2015)**	**Bergenstal (2013) ASPIRE In-Home**	**Secher 2013**
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)	Alfadhli, E., Osman, E., et al., 2016, Use of a real time continuous glucose monitoring system as an educational tool for patients with gestational diabetes *Diabetology and Metabolic Syndrome*, v. 8:48.	Wei Q, Sun Z, et al. 2016. Effect of a CGMS and SMBG on Maternal and Neonatal Outcomes in Gestational Diabetes Mellitus: a Randomized Controlled Trial. Nature Scientific reports. 6(87):1-9	Buckingham, BA; Raghinaru, D; et al. 2015. Predictive Low-Glucose Insulin Suspension Reduces Duration of Nocturnal Hypoglycemia in Children Without Increasing Ketosis. *Diabetes Care;* 38:1197–1204	Bergenstal, R. M., Klonoff, D. C., et al. 2013, Threshold-based insulin-pump interruption for reduction of hypoglycemia: *N. Engl. J Med*, v. 369, p. 224-232	Secher, A. L., Ringholm, L. et al. 2013, The effect of real-time continuous glucose monitoring in pregnant women with diabetes A randomized controlled trial: Diabetes Care, v. 36, p. 1877-1883.
Technology	RT-CGM	CGM	SAP-PLGS	SAP-LGS	RT-cgms
Reviewer	LS	LS	LS	LS	LS
Date	04/27/17	05/08/17	05/08/17	05/08/17	05/09/17
Section 1: Internal Validity					
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	YES	YES	YES	YES	YES
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	YES
1.3 The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	YES	YES	UNCLEAR	YES	YES
1.4 Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	UNCLEAR Blinding of pts not possible	NO Blinding of pts not possible. education management was not blinded; thus, the Hawthorne effect cannot be excluded.	PARTLY Patients blinded to PLGS allocation at night	NO However, Glycated hemoglobin levels were measured at a central laboratory	UNCLEAR blinding of physicians; Blinded real-time CGM was not performed in the control arm.
1.5 The intervention and control groups received the same care apart from the intervention(s) studied.	YES	YES	YES	YES	YES
1.6 The study had an appropriate length of follow-up.	YES	YES	YES	YES	YES
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES	YES	YES	YES	YES
1.8 What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did	4.6%	9.2%	1.2% dropped out; 4.9% failed to complete 42 nights follow-up	2.8% (7/247) withdrew before 3 months	3.2% (5/154); rt-CGM – 49/79 (62%) used intervention per protocol
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	YES	NO; per protocol analysis was also	The analysis followed a modified ITT	YES	YES

Description	Citations				
	Alfadhli 2016	**Wei 2016**	**Buckingham (2015)**	**Bergenstal (2013) ASPIRE In-Home**	**Secher 2013**
		conducted	principle		
1.10 All relevant outcomes are measured in a standard, valid and reliable way.	YES	YES	YES	YES	YES
1.11 The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	NO	NO	YES; glycemic control; ketosis.	NO	NO
1.12 The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	NO	NO	NO	NO	NO
1.13 Competing interests of members have been recorded and addressed.	YES	YES	YES	YES	YES
1.14 Views of funding body have not influenced the content of the study.	YES	YES	YES	YES. Independent data monitoring	YES
SECTION 2: External Validity					
2.1 How well was the study done to minimize bias? *Code Good, Fair, or Poor*	GOOD	GOOD	GOOD	GOOD	FAIR
2.2 If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	NA	NA	NA	NA	Independent data monitoring not performed but not expected to bias interpretation.
2.3 Are the results of this study directly applicable to the patient group targeted by this topic?	YES	YES	YES	YES	YES
2.4 Other reviewer comments:	Study may have been too small to show clinically important changes in outcomes.		Because randomization was nightly, HbA1c levels between intervention and control cannot be compared		RT-CGM compliance was lower than expected in pregnant women. Implications of this were discussed.

Abbreviations: ITT, intention-to-treat; NA, not applicable; PLGS, predictive low-glucose suspend; rt-cgm, real-time continuous glucose monitor; SAP, sensor augmented pump.

[a]As this study cannot be blinded to randomization for LGS ON or NO LGS FEATURE it is important that the endpoints of the study are not discussed with subjects beyond the goal of describing the efficacy and safety of the autonomous LGS system.

Table 21 Quality appraisal checklist for included Randomized Controlled trials (RCTs from 2012-2010)

Description	Citations					
	Battelino 2012 [SWITCH]	**Garg 2012**	**Bukara 2011**	**Hermanides 2011 [Eurythmics]**	**Bergenstal (2010) [STAR-3]**	**Kordonouri 2010 [ONSET]**
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)	Battelino, T., Conget, I., et al. 2012, The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomized controlled trial: *Diabetologia*, v. 55, p. 3155-3162.	Garg, S., Brazg, R. L., et al. 2012, Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study: *Diab. Tech & Therap.*: 205-209.	Bukara-Radujkovic, G., et al. 2011, Short-term use of continuous glucose monitoring system adds to glycemic control in young type 1 diabetes mellitus patients in the long run: a clinical trial: *Vojnosanitetski Pregled*:68: 650-654	Hermanides J, Nørgaard K, et al. 2011. Sensor-augmented pump therapy lowers HbA1c in suboptimally controlled Type1 diabetes; a randomized controlled trial. *Diabet Med*.28(10):1158-1167.	Bergenstal, RM., Tamborlane, WV et al. 2010, Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes: *New England Journal of Medicine,* v. 363, p. 311-320	Kordonouri, O., Pankowska, E., et al 2010. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: Results of the Pediatric Onset Study (ONSET) after 12 months of treatment: *Diabetologia,* v. 53, p. 2487-2495.
Technology	RT-CGM (& CSII)	SAP-LGS	CGM	SAP	CGM	SAP
Reviewer	LS	LS	LS	LS	LS	LS
Date	05/09/17	05/18/17	05/09/17	05/09/17	05/09/17	05/10/17
Section 1: Internal Validity						
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	YES	UNCLEAR	UNCLEAR	YES	YES	YES
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	UNCLEAR	UNCLEAR	UNCLEAR	YES	YES	UNCLEAR
1.3 The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	Cross-over study adult/children in separate arms	YES	NO; significant differences in age, diabetes duration & insulin dose at baseline	YES	YES Except for weight and student status	YES
1.4 Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	NO By its nature, the study precluded blinding. Participants, study staff and investigators were not blinded to the HbA1c data.	NO	UNCLEAR; single blind	NO By its nature, the study precluded blinding. For HbA1c determination in the central laboratory	NO Independent data management and statistical analyses	PARTLY All laboratory results were blinded to the investigators

Description	Citations					
	Battelino 2012 [SWITCH]	**Garg 2012**	**Bukara 2011**	**Hermanides 2011 [Eurythmics]**	**Bergenstal (2010) [STAR-3]**	**Kordonouri 2010 [ONSET]**
1.5 The intervention and control groups received the same care apart from the intervention(s) studied.	YES	YES	YES	YES More staff attention in SAP group during first half of study	YES	YES
1.6 The study had an appropriate length of follow-up.	YES	YES	YES; although CGM use was considered short	YES	YES	YES
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES	YES	YES	YES	YES	YES
1.8 What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did	9.8% (15/153) discontinued intervention; Excluded from analysis (n=6): no evaluable sensor data for either treatment sequence	0%	0%	5/83 (6.0%)	4(1%) lost to follow-up; 32(7%) discontinued; 6(1%) did not provide 1yr results	6/160 (3.8%)
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	YES	YES	YES	YES	YES	YES
1.10 All relevant outcomes are measured in a standard, valid and reliable way.	YES	YES	YES	YES	YES	YES
1.11 The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	NO	NO	NO	NO	NO	NO
1.12 The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	NO	NO	NO	NO	NO	NO
1.13 Competing interests of members have been recorded and addressed.	YES	YES	NO	YES	YES	YES
1.14 Views of funding body have not influenced the content of the study.	YES	YES	UNCLEAR	YES	YES	YES

Description	Citations					
	Battelino 2012 [SWITCH]	**Garg 2012**	**Bukara 2011**	**Hermanides 2011 [Eurythmics]**	**Bergenstal (2010) [STAR-3]**	**Kordonouri 2010 [ONSET]**
SECTION 2: External Validity						
2.1 How well was the study done to minimize bias? *Code Good, Fair, or Poor*	GOOD	GOOD	FAIR	GOOD	GOOD	GOOD
2.2 If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	NA	NA	This is unclear due to lack of consistent reporting; little discussion on potential bias	NA	NA	NA
2.3 Are the results of this study directly applicable to the patient group targeted by this topic?	YES	YES	UNCLEAR	YES	YES	YES
2.4 Other reviewer comments:	HbA1c was analyzed by a central laboratory		Issues with lack of reporting of results may have led to this study being down-graded; CGM use considered brief (3 days)	Medtronic had no role in the conduct of the analyses, interpretation of the data or in the decision to approve publication.		

Abbreviations: NA, not applicable; PLGS, predictive low-glucose suspend;

Table 22 Quality appraisal checklist for included Randomized Controlled trials (RCTs from 2009-2008)

Description	Citations					
	O'Connell, 2009	**Newman 2009 [MITRE]**	**Raccah, 2009 [RealTrend]**	**Hirsch 2008**	**Murphy 2008**	**Yoo 2008**
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)	O'Connell, M.A; Donath S; et al. 2009. Glycemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomized controlled trial *Diabetologia* 52:1250–1257	Newman, S. P., Cooke, D., et al. 2009, A randomized controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE): *Health Technology Assessment,* 13:iii-xi, 1	Raccah, D., Sulmont, V., et al. 2009, Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: The realtrend study: *Diabetes Care,* v. 32, p. 2245-2250.	Hirsch, I. B., Abelseth, J., et al. 2008, Sensor-augmented insulin pump therapy: Results of the first randomized treat-to-target study: *Diabetes Technology and Therapeutics,* v. 10, p. 377-383	Murphy, H. R., Rayman, G., et al. 2008, Effectiveness of continuous glucose monitoring in pregnant women with diabetes: Randomized clinical trial: *BMJ*, 337:907-910.	Yoo, H J., An, HG., et al. 2008, Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes*: Diabetes Research and Clinical Practice,* v. 82, p. 73-79.
Technology	SAP	CGM	SAP	SAP	CGM	RT-CGM
Reviewer	LS	LS	LS	LS	LS	LS
Date	05/10/17	05/10/17	05/10/17	05/10/17	05/10/17	05/11/17
Section 1: Internal Validity						
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	YES	YES	UNCLEAR	UNCLEAR	YES	YES
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	YES	UNCLEAR	UNCLEAR	UNCLEAR	YES	YES
1.3 The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	YES	YES	YES	YES	YES; Except for duration of diabetes	YES
1.4 Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	NO/ open label The nature of the intervention prevented participant blinding	NO open label	YES Physicians and patients were blinded to centralized A1C data from baseline to completion of the study	PARTLY all CGM data were blinded to the subjects during the 10 day run-in where baseline measurements made	NO Open label study	NO Open label study
1.5 The intervention and control groups received the same care apart from the intervention(s) studied.	YES	YES	YES	YES	YES	YES
1.6 The study had an appropriate length of follow-up.	YES	YES	YES	YES	YES	YES
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES	YES; standard care control did not have week 4, 8 or 12 measurements but	YES	YES	YES	YES – both 3 months; RT-CGM (once per month for 3 days at a time; SMBG at least 4x

Description	Citations					
	O'Connell, 2009	**Newman 2009 [MITRE]**	**Raccah, 2009 [RealTrend]**	**Hirsch 2008**	**Murphy 2008**	**Yoo 2008**
		included 26wk-18months				per week
1.8 What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did	7/62 (11.3%) withdrew consent	41 (10%) withdrew from the trial but 25 consented to HbA1c data (primary end point) being collected from routine clinic visits.	20/132 (15.2%) abandoned the study	8/146 (5.5%)	2/71 (2.8%) Withdrew from the CGM arm on or after first visit	8/65 (12.3%)
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	YES	YES	YES (partly); per protocol analyses also used	YES	YES	NO; per protocol analysis
1.10 All relevant outcomes are measured in a standard, valid and reliable way.	YES	YES	YES	YES	YES	ES
1.11 The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	NO	NO	NO	NO	NO	NO; but heavy reliance of surrogates;
1.12 The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	NO	NO	NO	NO	NO	NO
1.13 Competing interests of members have been recorded and addressed.	YES	YES	YES	YES	YES	YES
1.14 Views of funding body have not influenced the content of the study.	YES	YES	YES	YES	YES	YES
SECTION 2: External Validity						
2.1 How well was the study done to minimize bias? *Code Good, Fair, or Poor*	GOOD	GOOD	GOOD	GOOD	GOOD	GOOD
2.2 If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	NA	NA	NA	NA	NA	NA
2.3 Are the results of this study directly applicable to the patient group targeted by this topic?	YES	YES	YES	YES	YES	YES
2.4 Other reviewer comments:	Independent HbA1c analysis	Study commissioned by the HTA program UK			Study funded by the Ipswich Diabetes Centre Charity Research Fund UK.	

Abbreviations: NA, not applicable; PLGS, predictive low-glucose suspend;

Supporting references

Table 23 Quality appraisal checklist for supporting Randomized Controlled trials

Description	Citations		
	The DCCT (1993)	**Cordua (2013)**	**Battelino (2011)**
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)	The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986.	Cordua S, Secher AL, et al. 2013. Real-time continuous glucose monitoring during labour and delivery in women with Type 1 diabetes - observations from a randomized controlled trial. Diabet Med.;30(11):1374-1381.	Battelino T, Phillip M. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011;34(4):795-800.
Technology	Intensive Insulin therapy (with/without CSII) + SMBG	Real time-CGM	Real time-CGM
Reviewer	LS	LS	LS
Date	07/21/17	07/21/17	07/21/17
Section 1: Internal Validity			
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	YES	YES	YES
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	YES	YES	YES
1.3 The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	YES	YES	YES
1.4 Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	NO Blinding of pts not possible. No discussion provided.	NO	NO Because of its nature, the intervention could not be blinded, rendering the results less compelling.
1.5 The intervention and control groups received the same care apart from the intervention(s) studied.	YES	YES	YES
1.6 The study had an appropriate length of follow-up.	YES	YES	YES
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES	YES	YES
1.8 What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did	1% did not complete the 6.5yrs. 97% spent time receiving allocated treatment	45% women in the intervention arm used real-time continuous glucose monitoring during labour and delivery	The study was completed by 48 patients (83%) in the control group and 53 patients (85%), in the rt-CGM group.
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat	YES	YES	YES

Description	Citations		
	The DCCT (1993)	**Cordua (2013)**	**Battelino (2011)**
analysis)			
1.10 All relevant outcomes are measured in a standard, valid and reliable way.	YES	YES	YES
1.11 The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	NO	NO	NO
1.12 The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	NA	NA	NA
1.13 Competing interests of members have been recorded and addressed.	YES	YES	YES
1.14 Views of funding body have not influenced the content of the study.	YES	YES	UNLIKELY
SECTION 2: External Validity			
2.1 How well was the study done to minimize bias? *Code Good, Fair, or Poor*	GOOD	GOOD	GOOD
2.2 If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	NA	NA	NA
2.3 Are the results of this study directly applicable to the patient group targeted by this topic?	YES	YES	YES
2.4 Other reviewer comments:	This study shows the direct relationship between high intensity glucose management and a reduction in long term diabetes related complications.	Only pregnant women with type 1 diabetes were included in this study.	The results must be interpreted with caution since the patients and their families were highly motivated, demonstrating good metabolic control with an average of more than five blood glucose measurements per day before randomization,

Abbreviations: CSII, Continuous subcutaneous insulin infusion; DCCT, The Diabetes Control and Complications Trial; DCCT/EDIC, The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; NA, not applicable; PLGS, predictive low-glucose suspend;

Table 24 Quality appraisal checklist for supporting reviews

Citation			Kerr and Fayers (2008)	Wentholt (2007)	Dinapoli (2015)	Fonseca (2016)
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)			Kerr D, Fayers K. Continuous real-time glucose monitoring systems: time for a closer look. Pr Diab Int. 2008;25(1):37–41.	Wentholt I, Hoekstra J, De Vries J. Continuous glucose monitors: the long awaited watch dogs?. Diabetes Technol Ther. 2007;9(5):399–409.	Dinapoli TP. Diabetes in New York State. New York; 2015. https://www.osc.state.ny.us/reports/health/diabetes_2015.pdf .	Fonseca VA, Grunberger G, Anhalt H, et al. Continuous Glucose Monitoring: a Consensus Conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. Endocr Pract. 2016;22(8):1008-1021.
Technology			CGM	CGM	NA	CGM
Reviewer			LS	LS	LS	LS
Date			07/21/17	07/21/17	08/25/17	08/25/17
Section 1: Internal Validity	**1.1**	The study addresses an appropriate and clearly focused question.	NO/ this is a narrative review of the literature.	NO/ this is a narrative review of the literature.	NO/ this is a narrative review and report of the state of diabetes in NY	YES/ this report reviewed available CGM data with the aim of proposing strategies for expanding CGM access.
	1.2	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	No methods used. Narrative review of real time CGM technologies	No methods used. Narrative review of real time CGM technologies	No	NO
	1.3	The literature search is sufficiently rigorous to identify all the relevant studies.	None provided	None provided	None provided	None provided
	1.4	The criteria used to select articles for inclusion is appropriate.	None provided	None provided	None provided	None provided
	1.5	Study quality is assessed and taken into account.	No	No	No	NO
	1.6	There are enough similarities between the studies selected to make combining them reasonable.	No	No	No	NO
	1.7	Competing interests of members have been recorded and addressed.	YES	No	No	YES
	1.8	Views of funding body have not influenced the content of the study.	YES	YES	YES	YES

Citation			Kerr and Fayers (2008)	Wentholt (2007)	Dinapoli (2015)	Fonseca (2016)
Section 2: Overall Appraisal	**2.1**	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	Not applicable / this was a narrative review	Not applicable / this was a narrative review	Not applicable / this was a narrative review	Not applicable / This review was a summary of a conference on CGM
	2.2	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	NA	NA	NA	NA
	2.3	Are the results of this study directly applicable to the patient group targeted by this key question?	Supportive information only	Supportive information only	Supportive information only	Supportive information only
	2.4	Other reviewer comments	This paper was narrative review of CGM – innovations, mechanism of action, clinical trial results and future technologies.	This report offers an overview of the current applications and clinically relevant aspects of continuous glucose monitors (CGMs), e.g., the calibration procedure, interpretation of continuous glucose data, and some important limitations.	This report discusses the plan and current state of diabetes in NY state	**Please see statement below regarding this report

Abbreviations: CGM, Continuous glucose monitoring; LS, L Strachan; rtCGM, real-time Continuous glucose monitoring; NA, not applicable; NY, New York; SR, systematic reviews;

***This document represents the position of the American Association of Clinical Endocrinologists and the American College of Endocrinology Consensus Conference Writing Committee. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position and consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.*

Table 25 Quality appraisal checklist for supporting Economic Evaluations

Study ID		Roze (2015)	Fonda (2016)	Ly (2014)	Bronstone (2016)
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)		Roze S et al. Health-economic analysis of real-time continuous glucose monitoring in people with Type 1 diabetes. Diabet Med. 2015;32(5):618-626.	Fonda SJ et al. The Cost-Effectiveness of Real-Time Continuous Glucose Monitoring (RT-CGM) in Type 2 Diabetes. J Diabetes Sci Technol. 2016;10(4):898-904.	Ly TT et al. A cost-effectiveness analysis of sensor-augmented insulin pump therapy and automated insulin suspension versus standard pump therapy for hypoglycemic unaware patients with type 1 diabetes. Value Heal. 2014;17(5):561-569.	Bronstone A, et al. The Potential Cost Implications of Averting Severe Hypoglycemic Events Requiring Hospitalization in High-Risk Adults With Type 1 Diabetes Using RT Continuous Glucose Monitoring. J Diabetes Sci Technol. 2016;10(4): 905-913.
Technology:		RT-CGM	RT-CGM	SAP	RT-CGM
Checklist completed by: [date]		LS [08/08/17]	LS [08/08/17]	LS [08/09/17]	LS [08/08/17]
SECTION 1: APPLICABILITY					
1.1	The results of this study are directly applicable to the patient group targeted by this key question	YES SAP patient group	YES RT-CGM	YES	YES
1.2	The healthcare system in which the study was conducted is sufficiently similar to the system of interest in the topic key question(s).	NO Public funded health system	YES USA	NO Public funded health system	YES
SECTION 2: STUDY DESIGN, DATA COLLECTION, AND ANALYSIS					
2.1	The research question is well described.	YES	YES	YES	YES
2.2	The economic importance of the research question is stated.	YES	YES	YES	YES
2.3	The perspective(s) of the analysis are clearly stated and justified (e.g. healthcare system, society, provider institution, professional organization, patient group).	YES - societal payer perspective	YES US third-party payer perspective	YES Australian health care system perspective	YES US commercial health plan
2.4	The form of economic evaluation is stated and justified in relation to the questions addressed.	YES	YES	YES	YES Cost analysis only
2.5	*Pick one* a. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies). b. Details of the design and results of effectiveness study are given (if based on a single study).	a. YES	b. YES	b. YES	NO
2.6	Estimates of effectiveness are used appropriately.	YES	YES	YES	NA
2.7	Methods to value health states and other benefits are	UNCLEAR	YES	UNCLEAR	NA

Study ID		Roze (2015)	Fonda (2016)	Ly (2014)	Bronstone (2016)
	stated.				
2.8	Outcomes are used appropriately.	YES	YES	YES	YES
2.9	The primary outcome measure for the economic evaluation is clearly stated.	YES	NOT one Primary measure – use LE & QALE	YES	YES
2.10	Details of the subjects from whom valuations were obtained are given.	YES	YES	YES	NO
2.11	Competing alternatives are clearly described.	YES	YES	YES	YES
2.12	All important and relevant costs for each alternative are identified.	YES	YES	YES	YES
2.13	Methods for the estimation of quantities and unit costs are described.	YES	YES	YES	YES
2.14	Quantities of resource use are reported separately from their unit costs.	UNCLEAR	YES	YES	YES
2.15	Productivity changes (if included) are reported separately.	YES	UNCLEAR	NA	NA
2.16	The choice of model used and the key parameters on which it is based are justified.	YES	YES	YES	NA
2.17	All costs are measured appropriately in physical units.	YES	YES	YES	NA
2.18	Costs are valued appropriately.	YES	YES	YES	YES
2.19	Outcomes are valued appropriately.	YES	YES	YES	YES
2.20	The time horizon is sufficiently long enough to reflect all important differences in costs and outcomes.	YES	YES	UNCLEAR – 6 months is a limitation	UNCLEAR – annual costs
2.21	The discount rate(s) is stated.	YES	YES	NA	NA
2.22	An explanation is given if costs and benefits are not discounted.	YES	NA	YES	NA
2.23	The choice of discount rate(s) is justified.	YES	NO	NA	NA
2.24	All future costs and outcomes are discounted appropriately.	YES	YES	NA	NA
2.25	Details of currency of price adjustments for inflation or currency conversion are given.	YES	YES	NA	NA
2.26	Incremental analysis is reported or it can be calculated from the data.	YES	YES	YES	NO
2.27	Details of the statistical tests and confidence intervals are given for stochastic data.	YES	NA	YES	NO
2.28	Major outcomes are presented in a disaggregated as well as aggregated form.	NA	NA	NA	NO
2.29	Conclusions follow from the data reported.	YES	YES	YES	YES
2.30	Conclusions are accompanied by the appropriate caveats.	YES	YES	YES	YES

Study ID		Roze (2015)	Fonda (2016)	Ly (2014)	Bronstone (2016)
SECTION 3: SENSITIVITY ANALYSIS					
3.1	The approach to sensitivity analysis is given.	YES	YES – no details	YES	NA
3.2	All important and relevant costs for each alternative are identified.	YES	NO	YES	NA
3.3	An incremental analysis of costs and outcomes of alternatives is performed.	YES	YES	YES	NA
3.4	The choice of variables for sensitivity analysis is justified.	YES	NO	NO	NA
3.5	All important variables, whose values are uncertain, are appropriately subjected to sensitivity analysis.	YES	NO	YES	NA
3.6	The ranges over which the variables are varied are justified.	YES	NO	NO	NA
SECTION 4: CONFLICT OF INTEREST					
4.1	Competing interests of members have been recorded and addressed.	YES	YES	YES	YES
4.2	Views of funding body have not influenced the content of the study.	YES	YES	YES	YES
SECTION 5: OVERALL ASSESSMENT					
5.1	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	GOOD	GOOD	GOOD	FAIR
5.2	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	NA	NA	NA	Costing study only. Biases unlikely to affect results
5.3	Other reviewer comments:	Well conducted CEA using the CORE Diabetes Model	-	-	

Abbreviations: CEA, cost-effectiveness analysis; LE, Life expectancy; QALE, quality-adjusted life expectancy

Table 26 Quality appraisal checklist for supporting cohort studies

Study ID			Garg (2017)	Boland (2001)	Miller (2015)	Wong (2014)	DCCT/EDIC (2005)
Study identification (*Include author, title, year of publication, journal title, pages*)			Garg SK, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017;19(3):1-9.	Boland E et al. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care. 2001;24(11):1858–1862.	Miller KM, et al. Current state of type 1 diabetes treatment in the U.S.: Updated data from the t1d exchange clinic registry. Diabetes Care. 2015;38(6):971-978.	Wong JC, et al. Real-time continuous glucose monitoring among participants in the T1D exchange clinic registry. Diabetes Care. 2014;37(10):2702-2709.	The Diabetes Control and Complications Trial Research/ Epidemiology of Diabetes Interventions and Complications Study Research Group. Intensive Diabetes Treatment and Cardiovascular disease in Patients with Type 1 diabetes. N Engl J Med. 2005;353(25):2643-2653.
Technology			CGM	CGM	Advanced diabetes technologies	CGM	Intensive therapy (w/without insulin pump)
Reviewer			LS	LS	LS	LS	LS
Date			07/21/17	07/21/17	08/9/17	08/9/17	08/9/17
Section 1: Internal Validity	**1.1**	The study addresses an appropriate and clearly focused question.	YES	YES	YES	YES	YES
	1.2	**SELECTION OF SUBJECTS** The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	YES	NA	NA	NA	YES
	1.3	The study indicates how many of the people asked to take part did so in each of the groups being studied.	NA	NO	NA	NA	NO
	1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and accounted for in the analysis.	NA	NA	NA	NA	YES
	1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	Of the 129 subjects enrolled, there were two screen failures and four withdrawals (a withdrawal rate of less than 5%).	NONE	NA single cohort/ divided into age groups	NA – single cohort/ divided into age groups	NO
	1.6	Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.	NO	NA	NA – retrospective registry data analysis	NA – retrospective registry data analysis	NO
	1.7	**ASSESSMENT AND FOLLOW-UP** The study employed a precise definition	YES	YES	YES	YES	YES

Study ID			Garg (2017)	Boland (2001)	Miller (2015)	Wong (2014)	DCCT/EDIC (2005)
		of outcome(s) appropriate to the key question(s).					
	1.8	The assessment of outcome(s) is made blind to exposure status.	NO	NO	NO	NO	Masked adjudication of events
	1.9	Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	NO	NO	NO	NO	YES
Section 1: Internal Validity	**1.10**	The measure of assessment of exposure is reliable.	YES (exposure in this case is CGM)	YES	YES (exposure in this case are the interventions)	YES CGM use is exposure of interest	YES
	1.11	Exposure level or prognostic factor is assessed more than once.	YES	YES	NA	Yes Description of CGM use	YES
	1.12	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	YES	YES	NO	NO	YES
	1.13	The study had an appropriate length of follow-up.	YES	NO – 3 days only	YES – 1 yr data	YES	YES
	1.14	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	YES	NA	YES	YES	YES
	1.15	**CONFOUNDING** The main potential confounders are identified and taken into account in the design and analysis.	NO	NO	NO	YES	YES
	1.16	**STATISTICAL ANALYSIS** Have confidence intervals been provided?	YES	NO	NO	YES	YES
	1.17	**CONFLICT OF INTEREST** Competing interests of members have been recorded and addressed.	YES	YES	YES	YES	YES
	1.18	Views of funding body have not influenced the content of the study.	NA	YES	YES	YES	YES

Study ID			Garg (2017)	Boland (2001)	Miller (2015)	Wong (2014)	DCCT/EDIC (2005)
Section 2: Overall Appraisal	**2.1**	How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code Good, Fair, or Poor*	GOOD	FAIR	FAIR	GOOD	GOOD
	2.2	If coded as fair or poor, what is the likely direction in which bias might affect the study results?	NA	Unlikely that the bias in this small study would have altered the direction of the results significantly.	Unlikely to affect direction of results.	NA	NA
	2.3	Are the results of this study directly applicable to the patient group targeted by this key question?	Indirectly applicable as did not sit our inclusion criteria (single arm) – but examined HCL systems	Indirectly applicable as did not sit our inclusion criteria (single arm) – but examined CGM in small cohort of pediatric patients	Indirectly applicable	Indirectly – as it examined real world use of CGM. However this study was not part of our included studies as it did not fit our PICO/ inclusion criteria	Indirectly. Intensive diabetes management can be achieved with CGM. This study did not directly compare CGM technologies.
	2.4	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study are you certain that the overall effect is due to the exposure being investigated?	YES	YES	YES	YES	YES
	2.5	Other reviewer comments:	Single arm interventional study of good quality	Small pilot study with important conclusions directly relevant to the use of CGM in children.	Retrospective registry study with large type 1 cohort.	Some issues with generalizability of these results despite its observational nature.	Very important study linking the benefits of achieving near normoglycemia in T1D and the long term benefits on patient outcomes.

Abbreviations: CGM, continuous glucose monitoring; HCL, Hybrid closed loop system; NA, not applicable; T1D, type-1 diabetes

Appendix D: Characteristics of RCTs

Alfadhli 2016[27]

Design	PROSPECTIVE OPEN-LABEL RANDOMIZED CONTROLLED CLINICAL TRIAL
Stated aim of study	*The purpose of this study was to evaluate the impact of a single application RT-CGMS on maternal glycemic control and pregnancy outcomes for patients with GDM in comparison to the standard care and to assess its usefulness as an educational and motivational tool*.
Participants	**WHO PARTICIPATED**: 130 pregnant women diagnosed with GDM attending antenatal services at Maternity and Children Hospital, Madinah, Saudi Arabia from October 2011 to June 2014 were included in the study. RT-CGM group (n=68 ITT); SMBG (n=62, ITT) **INSULIN PUMP USERS**: 0% **SEX**: 100% pregnant females **AGE** (mean years (SD)): CGM group 34.15 (5.04) (11.9), control 32.93 (5.70) **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** N/A [redacted] **CRITERIA**: diagnosed with GDM in the current pregnancy, had a singleton pregnancy, planned to give birth at the study hospital and were able to give written consent to participate. **EXCLUSION CRITERIA**: pre-existing diabetes, multiple pregnancies, chronic diseases and drugs that might affect pregnancy outcome. **DIAGNOSTIC CRITERIA**: The diagnosis of GDM was based on the recommendations of the International Association of Diabetes in Pregnancy Study Groups (IADPSG). **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A. **DURATION OF INTERVENTION**: once for 3–7 days, within 2 weeks of GDM diagnosis **DURATION OF FOLLOW-UP**: until delivery **RUN-IN PERIOD**: N/A **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 1 **COUNTRY**: Saudi Arabia **SETTING**: outpatients **CGMSYSTEM**: SMBG & Guardian® REAL-Time Continuous Glucose Monitoring System (Medtronic MiniMed) **CONTROL**: SMBG alone
Outcomes	**PRIMARY**: Maternal glycemic control and pregnancy outcomes **SECONDARY**: Changes in parameters of glucose variability, which includes mean sensor readings, standard deviation (SD) of blood glucose, and area under the curve for hyper and hypoglycemia at the end of the RT-CGMS application.
RESULTS	
Primary & Secondary Outcome	• There were no significant differences between the two groups. • Baseline HbA1c and glucose levels at fasting, 1 and 2-h during OGTT (oral glucose tolerance test) were comparable. • There was significant improvement in the parameters of glucose variability by the last day of sensor application. • Both mean sensor glucose and SD of the sensor glucose were reduced significantly, P = 0.016 and P = 0.034, respectively • HbA1c, mean fasting and postprandial glucose level were comparable between the two groups at the end of the pregnancy. • In addition, there were no significant differences in the number of women who required

	insulin therapy or the total daily insulin dose between both groups, • Of the 122 pregnancies, there was one miscarriage and 121 live births • Five infants had congenital malformations, with three cardiovascular malformations in the SMBG group and two in the RT-CGM group (one cardiovascular and one anus malformation). • Approximately half of the deliveries were by caesarean section with no differences between the two groups. • Similarly, there were no differences in the gestational age at deliveries, birth weight, prevalence of macrosomia and neonatal hypoglycemia. • There were no statistically significant differences in the other maternal and neonatal outcomes between the two groups
Adverse Events	• RT-CGMS was generally well tolerated and there were no major side effects aside from mild erythema and skin irritation around the sensor's insertion site. • Indeed, the majority of patients (90 %) accepted the RT-CGMS.
Stated conclusions	A single application of RT-CGMS is useful as an educational and a motivational tool for patients with GDM and helps in improving blood glucose variability. However, these changes are not coupled with improvement in HbA1c and pregnancy outcomes. Using RT-CGMS, similar to any other technology, requires sensible utilization of the device to obtain the greatest benefit from the system and the key factor in achieving success is selecting appropriate patients.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: No (This work was supported by a Grant, number AT-30-362, from Taibah University, Medina, Saudi Arabia.) **PUBLICATION STATUS**: Peer review journal

Wei 2016[28]

Design	**PROSPECTIVE OPEN-LABEL RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	*In this study, we sought to investigate the effects of a continuous glucose monitoring system (CGMS) on maternal and neonatal outcomes*
Participants	**WHO PARTICIPATED**: 106 women with gestational diabetes mellitus (GDM) in gestational weeks 24–28 were randomly allocated to the antenatal care plus CGMS group (n=55) or the self-monitoring blood glucose (SMBG, n=62) **INSULIN PUMP USERS**: 0% **SEX**: 100% pregnant females **AGE** (mean years (SD)): CGM 30.29 (3.60); group control 29.96 (3.43)•} **ETHNIC GROUPS**: N/A. **DURATION OF DISEASE** N/A **INCLUSION CRITERIA**: between 24 and 28 weeks gestation with a singleton pregnancy, a positive oral glucose challenge result, and written informed consent. **EXCLUSION CRITERIA**: a diagnosis of diabetes mellitus, previous treatment for GDM, presence of infection, or other severe metabolic, endocrine, medical or psychological comorbidities. **DIAGNOSTIC CRITERIA**: the pregnant women were defined as having GDM if they had at least one abnormally high plasma glucose value out of the three measurements in the 75 g OGTT (fasting > 92 mg/dL (5.1 mmol/L), 1 h > 180 mg/dL (10.0 mmol/L), or 2 h > 153 mg/dL (8.5 mmol/L)). **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A. **DURATION OF INTERVENTION**: N/A **DURATION OF FOLLOW-UP**: unclear (mention of 6 weeks post partum) **RUN-IN PERIOD**: N/A **STUDY TERMINATED BEFORE REGULAR END**: no

Interventions	**STUDY CENTRES**: 1 **COUNTRY**: China **SETTING**: outpatients **CGM SYSTEM**: CGMS (Gold Medtronic MiniMed, Northridge, CA, USA). **CONTROL**: SMBG alone
Outcomes	**PRIMARY**: obstetrical and neonatal outcomes - caesarean section, birth weight, standard deviation of weight for gestational weeks, and Apgar score at 5 min **SECONDARY** HbA1c levels; Glycemic control;
RESULTS	
OUTCOMES:	• The caesarean delivery rate was greater in the SMBG group than in the CGMS group, but the difference was not statistically significant (69% vs. 60%, P = 0.37). • No perinatal deaths were observed in either group. • Gestational weeks at delivery, Apgar score at 5 min, macrosomia, neonatal hypoglycemia, and extreme LGA (≥ 97.7th percentile) and SGA (≤ 10th percentile) were not significantly different between the two groups. • Fewer LGA (≥ 90th percentile) infants were born to mothers in the CGMS group than to those in the SMBG group, but the difference was not statistically significant (35.3% vs. 52.7%, *P* = 0.071). • HbA1C levels dropped slowly during the gestation period from baseline in both the CGMS and SMBG groups (5.7% •± 0.34% vs. 5.8% •± 0.29%, *P* = 0.096). • Compared to those in the SMBG group, HbA1C levels were lower in the CGMS group but were not significantly different throughout the last two trimesters.
Adverse events	• The continuous glucose monitor was commonly well tolerated by the pregnant women in the CGMS group. • No skin infections occurred at the sensor insertion site, but mild erythema, itchiness, and inflammation often occurred.
Stated conclusions	This study proved that the CGMS, especially when initiated early, provides benefits in conjunction with a professional healthcare system to reduce maternal weight gain and glycemic variability. Extensive clinical studies are warranted to test the effectiveness of CGMS management of maternal weight gain in reducing perinatal problems, especially fetal macrosomia, in GDM women.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: no **PUBLICATION STATUS**: Peer review journal

Buckingham (2015)[29]

Design	**RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	*Nocturnal hypoglycemia can cause seizures and is a major impediment to tight glycemic control, especially in young children with type 1 diabetes. We conducted an in-home randomized trial to assess the efficacy and safety of a continuous glucose monitor–based overnight predictive low-glucose suspend (PLGS) system.*
Participants	**WHO PARTICIPATED**: Children with type 1 diabetes in two age-groups; 11–14 (n=45) and 4–10 years of age (n=36) **INSULIN PUMP USERS**: 100% **SEX**: 11-14 yrs group (56% male), 4-10yrs (46% male) **AGE** (median) 11-14 yrs group (13), 4-10yrs (8 yrs) **ETHNIC GROUPS**: 11-14 yrs group (96% Caucasian), 4-10yrs (95% Caucasian) **DURATION OF DISEASE** (median years): 11-14 yrs group (6 years), 4-10yrs (3 years) **INCLUSION CRITERIA**: major eligibility criteria were type 1 diabetes with use of daily insulin therapy for ≥1 year and an insulin infusion pump for ≥6months and a glycated hemoglobin

	(HbA1c) level measured with a point-of-care device ≤8.5% (69 mmol/mol). **EXCLUSION CRITERIA**: N/A **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A. **DURATION OF INTERVENTION**: continuous **DURATION OF FOLLOW-UP**: 42 nights **RUN-IN PERIOD**: 10–15 days **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 3 **COUNTRY**: USA **SETTING**: in-home **CGMSYSTEM**: MiniMed Paradigm REAL-Time Veo System with Enlite glucose sensor (Medtronic Diabetes) - hypoglycemia prediction algorithm in operation at night (intervention night) **CONTROL**: MiniMed Paradigm REAL-Time Veo System with Enlite glucose sensor (Medtronic Diabetes) - hypoglycemia prediction algorithm NOT ACTIVATED at night (control night)
Outcomes	**PRIMARY OUTCOME:** The primary outcome was percent time < 70 mg/dL pooled across nights. **SECONDARY OUTCOME:** Comparison of the frequency of intervention versus control nights with at least one CGM glucose value ,60 mg/dL. **SAFETY OUTCOMES:** Morning blood glucose and ketone levels.
RESULTS	
Primary outcome	**4-10 yrs group:** • Median percent time <70 mg/Dl was reduced by 50% from 6.2% (IQR 3.0, 7.6) during control nights to 3.1% (IQR 1.6, 5.0) during intervention nights (P < 0.001) **11-14 yrs group:** • Median percent time <70 mg/dL was reduced by 54% from 10.1% (IQR 5.9,13.8) during control nights to 4.6% (IQR 2.9, 7.3) during intervention nights (P<0.001)
Secondary outcome	**4-10 yrs group:** • <60 mg/dL occurred on 24% of control nights vs. 19% of intervention nights (P =0.01). • Overnight mean glucose was higher on intervention than on control nights (mean 160 mg/dL vs. 153 mg/dL, P = 0.004). • Mean time in the target range of 70–180 mg/dL was 63% in both arms (P = 0.50), median time >180 mg/dL was 32% vs. 31% (P = 0.23), and median time >250 mg/dL was 6% vs. 7% (P = 0.77) on intervention versus control nights, respectively **11-14 yrs group:** • At least one CGM glucose reading <60 mg/dL occurred on 29% of control nights vs. 21% of intervention nights (P < 0.001). • Overnight mean glucose was higher on intervention nights than on control nights (mean 152 vs. 144 mg/dL, P < 0.001).
Safety Outcomes	**4-10 yrs group:** • At least one hypoglycemic event with CGM glucose >60 mg/dL continuously for >120 min occurred on 5% of control nights vs. 1% of intervention nights (P < 0.001), with similarly significant reductions for events lasting at least 10 and 25 min. • Mean ± SD morning blood glucose was 158 ± 22 mg/dL following intervention nights vs. 154 ± 25 mg/dL following control nights (P = 0.11). • The frequencies of elevated morning urine or blood ketones were higher than those in the 11–14-year-old group but similar in the two treatment arms. **11-14 yrs group:** • At least one hypoglycemic event with CGM glucose >60 mg/dL continuously for >120 min occurred on 8% of control nights vs. 3% of intervention nights (P > 0.001)

	• Mean ± SD morning blood glucose was 176 ± 28 mg/dL following intervention nights vs. 159 ± 29 mg/dL following control nights (P <0.001) • The frequency of elevated morning urine or blood ketones was low and similar in the two treatment arms.
Stated conclusions	In 4–14-year-olds, use of a nocturnal PLGS system can substantially reduce overnight hypoglycemia without an increase in morning ketosis, although overnight mean glucose is slightly higher.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: no **PUBLICATION STATUS**: Peer review journal

Bergenstal (2013)[30] ASPIRE In-Home

Design	**PROSPECTIVE RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	We evaluated sensor-augmented insulin-pump therapy with and without the threshold-suspend feature in patients with nocturnal hypoglycemia.
Participants	**WHO PARTICIPATED**: A total of 247 patients with T1DM were randomly assigned to receive sensor-augmented insulin pump therapy with the threshold-suspend feature (threshold-suspend group, 121 patients) or standard sensor-augmented insulin-pump therapy (control group, 126 patients). **SEX**: Threshold suspend group: 38% male; Control group: 39.7% male **AGE** (mean age (SD)): Threshold suspend group: 41.6 (12.8); Control group: 44.8 (13.8) **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** (mean years (SD)): Threshold suspend group: 27.1 (12.5); Control group: 26.7 (12.7) **INCLUSION CRITERIA**: Eligible patients were 16 to 70 years of age and had type 1 diabetes of at least 2 years' duration, had a glycated hemoglobin value of 5.8 to 10.0%, and had used insulin-pump therapy for more than 6 months. **EXCLUSION CRITERIA**: Patients were excluded if they had had more than one episode of severe hypoglycemia (resulting in coma or seizures or requiring medical assistance) in the previous 6 months; were pregnant; had received thyroid disease, or chronic renal disease in the previous 12 months; had been hospitalized or had visited the emergency room for symptoms related to uncontrolled diabetes in the previous 6 months; or had red-cell disease affecting glycation of hemoglobin. a diagnosis of macrovascular disease. **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: sensor to be worn daily **DURATION OF FOLLOW-UP**: 3 months **RUN-IN PERIOD**: 2 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: N/A **COUNTRY**: USA **SETTING**: in-home **CGM SYSTEM**: Paradigm Veo insulin pump (Medtronic) with its threshold-suspend feature **CONTROL**: Paradigm Revel 2.0 insulin pump (Medtronic), which does not have the threshold-suspend feature
Outcomes	**PRIMARY OUTCOMES:** The primary safety outcome was the change in the glycated hemoglobin level. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemic events. **SECONDARY OUTCOMES:** the percentage of sensor glucose values that were less than 70 mg per deciliter, rates of hypoglycemic events, characteristics of automatic pump-suspension

	events, and quality-of-life and treatment related measures.
RESULTS	
PRIMARY OUTCOMES:	• The changes in glycated hemoglobin values were similar in the two groups. • The mean AUC for nocturnal hypoglycemic events was 37.5% lower in the threshold suspend group than in the control group (980±1200 mg per deciliter [54.4±66.6 mmol per liter] × minutes vs. 1568±1995 mg per deciliter [87.0±110.7 mmol per liter] × minutes, P<0.001).
SECONDARY OUTCOMES:	• Nocturnal hypoglycemic events occurred 31.8% less frequently in the threshold-suspend group than in the control group (1.5±1.0 vs. 2.2±1.3 per patient week, P<0.001). • The percentages of nocturnal sensor glucose values of less than 50 mg per deciliter (2.8 mmol per liter), 50 to less than 60 mg per deciliter (3.3 mmol per liter), and 60 to less than 70 mg per deciliter (3.9 mmol per liter) were significantly reduced in the threshold-suspend group (P<0.001 for each range). • After 1438 instances at night in which the pump was stopped for 2 hours, the mean sensor glucose value was 92.6±40.7 mg per deciliter (5.1±2.3 mmol per liter). • Four patients (all in the control group) had a severe hypoglycemic event; no patients had diabetic ketoacidosis.
Stated conclusions	This study showed that over a 3-month period the use of sensor-augmented insulin pump therapy with the threshold-suspend feature reduced nocturnal hypoglycemia, without increasing glycated hemoglobin values.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic MiniMed **PUBLICATION STATUS**: Peer review journal

Secher 2013[31]

Design	**PROSPECTIVE RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	To assess whether intermittent real-time continuous glucose monitoring (CGM) improves glycemic control and pregnancy outcome in unselected women with pre-gestational diabetes.
Participants	**WHO PARTICIPATED**: A total of 123 pregnant women with type 1 diabetes and 31 women with type 2 diabetes were randomized to use real-time CGM f or 6 days at 8, 12, 21, 27, and 33 weeks in addition to routine care, including self-monitored plasma glucose seven times daily, or routine care only. **SEX**: 100% pregnant females **AGE** (mean age (range)): real time CGM group: 32 (21–42); Control group: 31 (19–43) **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** (mean years (range)): real time CGM group: 10 (1–37); Control group: 12 (1–38) **INCLUSION CRITERIA**: During the study period of 15 February 2009 to 15 February 2011, all Danish speaking pregnant women with pre-gestational diabetes referred to the Center for Pregnant Women with Diabetes, Rigshospitalet, before 14 completed gestational weeks with one living intrauterine fetus (n = 222), were offered participation in the study **EXCLUSION CRITERIA**: Exclusion criteria were present use of real-time CGM(n = 7), severe mental or psychiatric barriers (n = 4), diabetic nephropathy (n = 3), or severe concurrent comorbidity **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: 30 women received antihypertensive treatment, mainly methyldopa (n = 27). Eight women were treated with antidepressive medicine-six of them with selective

	serotonin reuptake inhibitors. Thyroid dysfunction was treated in 32 women with levothyroxine (n = 29), thiamazole (n= 2), or propylthiouracil (n = 1), resulting in normal thyroid function in all women. **DURATION OF INTERVENTION**: intermittent use of CGM for 6 days at the first pregnancy visit at 8 weeks and at 12, 21, 27 and 33 weeks **DURATION OF FOLLOW-UP**: shortly after delivery **RUN-IN PERIOD**: 2 weeks **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: N/A **COUNTRY**: Denmark **SETTING**: out-patients **CGM SYSTEM**: Guardian Real-time Continuous Glucose Monitoring System with the Sof-Sensor; Medtronic MiniMed, Northridge, CA & routine pregnancy care **CONTROL**: routine pregnancy care
Outcomes	**PRIMARY OUTCOMES:** The prevalence of large-for-gestational-age infants [i.e., infant birth weight ≥90th centile adjusted for sex and gestational age **SECONDARY OUTCOMES:** The prevalence of preterm delivery (,37 weeks of gestation) and/or severe neonatal hypoglycemia (2-h plasma glucose ,2.5 mmol/L treated with intravenous glucose infusion); miscarriage (before 22 weeks), preeclampsia [blood pressure ≥140/90 and proteinuria (29)], birth weight SD score (z-score), neonatal hypoglycemia (2-h plasma glucose <2.5 mmol/L), and major congenital malformation (i.e., abnormality requiring surgery and/or resulting in permanent injury).
RESULTS	
OUTCOMES:	The prevalence of large-for-gestational-age infants (45 vs. 34%; P = 0.19) and other perinatal outcomes were comparable between the arms.
Stated conclusions	In this randomized trial, intermittent use of real-time CGM in pregnancy, in addition to self-monitored plasma glucose seven times daily, did not improve glycemic control or pregnancy outcome in women with pre-gestational diabetes.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: no **PUBLICATION STATUS**: Peer review journal

Battelino [SWITCH] 2012[32]

Design	**PROSPECTIVE RANDOMIZED CONTROLLED CROSSOVER TRIAL**
Stated aim of study	To determine the efficacy of adding continuous glucose monitoring (CGM) to insulin pump therapy (CSII) in type 1 diabetes.
Participants	**WHO PARTICIPATED**: Children and adults (n=153) on CSII with HbA1c 7.5–9.5% (58.5–80.3 mmol/mol) were randomized to (CGM) a Sensor On or Sensor Off arm for 6 months. **SEX**: Sequence ON/OFF (54% male); Sequence OFF/ON (49% male) **AGE** (mean age (sd)): Sequence ON/OFF 28 (16); Sequence OFF/ON 28 (17) **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** (mean years (sd)): Sequence ON/OFF 16 (12); Sequence OFF/ON 14 (10) **INCLUSION CRITERIA**: Participants were included if they were aged between 6 and 70 years, had a type 1 diabetes duration of more than 1 year and a HbA1c level between 7.5% and 9.5% (58.5 and 80.3 mmol/mol). In addition, eligible participants had been using CSII with rapid-acting insulin analogues for more than 6 months, were naive to CGM and had successfully completed a five-question multiple choice test concerning pump therapy and general understanding of diabetes. **EXCLUSION CRITERIA**: Exclusion criteria included ≥3 incidents of severe hypoglycemia in the last 12 months, a history of hypoglycemia unawareness (i.e. hypoglycemia without

	symptoms), concomitant chronic disease known to affect diabetes control and any pharmacological treatment that might modify glycemic values. **DIAGNOSTIC CRITERIA**: N/A. **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: **DURATION OF INTERVENTION**: N/A **DURATION OF FOLLOW-UP**: 6 months **RUN-IN PERIOD**: 1 month **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 8 **COUNTRY**: Europe **SETTING**: out-patients **CGM SYSTEM**: (Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland), Sensor ON **CONTROL**: Guardian REAL-Time Clinical; Medtronic, Tolochenaz, Switzerland), Sensor OFF
Outcomes	**PRIMARY OUTCOMES:** The difference in HbA1c levels between the Sensor On and Sensor Off arms. **SECONDARY OUTCOMES:** Changes in glycemic patterns, as expressed by mean 24 h glucose and 24 h AUC values, and changes in the time spent in hypoglycemia (<3.9 mmol/l), hyperglycemia (>10 mmol/l) and euglycemia (3.9–10 mmol/l).
RESULTS	
PRIMARY OUTCOMES	• After 6 months' treatment, the mean HbA1c level was 8.04% (64.34 mmol/ mol) in the Sensor On arm and 8.47% (69.08 mmol/mol) in the Sensor Off arm; • The mean difference between arms was −0.43% (−4.74 mmol/mol) (95% CI −0.32%, −0.55% [−3.50, −6.01 mmol/mol]; p<0.001). • The HbA1c level decreased continuously during the 6-month Sensor On arm, and withdrawal of the sensor for the On/Off sequence resulted in glycemic control reverting towards baseline levels during the 4-month washout period • Mean sensor use was 80% (median 84%) of the required time (mean 81% over the final 4 weeks). The decrease in HbA1c was smaller in the group that used the sensor <70% of the required time (mean±SD: −0.24±1.11% [−2.6±12.1 mmol/mol]; p00.03) than in the group that used it ≥70% of the required time (−0.51±0.07% [−5.6± 0.76 mmol/mol]; p<0.001).
SECONDARY OUTCOMES	• Time spent with a sensor glucose level <3.9 mmol/l was significantly less during the Sensor On period compared with the Sensor Off period (19 vs 31 min/day, respectively; p=0.009). • In addition, significant differences in the average daily time spent in euglycemia (3.9–10 mmol/l) and hyperglycemia (>10 mmol/l) were observed in favor of the Sensor On arm. • The average daily glucose level was significantly lower in the Sensor On arm compared with the Sensor Off arm (8.82 vs 9.44 mmol/l; p<0.001) and the average daily AUC for glucose levels in the euglycemic (3.9–10 mmol/l), hypoglycemic (<3.9 mmol/l) and hyperglycemic (>10 mmol/l) ranges were significantly lower in the Sensor On group. • Glycemic variability was significantly lower during the Sensor On period when calculated as 24 h SD of the mean glucose, but there was no significant difference when assessed by the mean amplitude of glycemic excursions (MAGE). • The median number of finger-stick blood glucose tests performed by the participants also decreased significantly in the Sensor On arm compared with the Sensor Off arm (4.9 vs 5.5; p<0.001).
Stated conclusions	Both pediatric and adult participants with type 1 diabetes using CSII therapy alone, the addition of CGM resulted in an improvement in HbA1c with a concomitant decrease in time spent in hypoglycemia. More frequent self-adjustments of insulin therapy with SAP may have contributed to these effects. The removal of CGM resulted in a loss of metabolic benefit.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Yes, International Trading Sarl, Tolochenaz, Switzerland.

	PUBLICATION STATUS: Peer review journal

Garg 2012[33]

Design	**RANDOMIZED CROSSOVER CLINICAL TRIAL**
Stated aim of study	The in-clinic ASPIRE (Automation to Simulate Pancreatic Insulin REsponse) study was undertaken to quantitatively determine the efficacy of the system's LGS feature combined with the Sof-Sensor_ (Medtronic MiniMed, Inc.) glucose sensor in reducing severity and duration of hypoglycemia in a setting of carefully monitored exercise
Participants	**WHO PARTICIPATED**: Subjects 17–58 years of age with type 1 diabetes for at least 1 year and at least 3 months of experience with a Medtronic insulin pump system were recruited to LGS feature ON (n=25) or LGS feature off (n=25) before crossing over.. **INSULIN PUMP USERS**: 100% **AGE** (mean years (SD)): LGS ON/OFF grp 34.5 (12.2), LGS OFF/ON grp 34.1 (12.7) **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** N/A. **INCLUSION CRITERIA**: Subjects 17–58 years of age with type 1 diabetes for at least 1 year and at least 3 months **EXCLUSION CRITERIA**: N/A **DIAGNOSTIC CRITERIA**: N/A. **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: continuous CGM during the study period **DURATION OF FOLLOW-UP**: duration of hypoglycemic period 4hrs **RUN-IN PERIOD**: washout periods lasting 3–10 days before cross over **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: unclear **COUNTRY**: USA **SETTING**: in-clinic **CGMSYSTEM**: Paradigm sensor-augmented pump therapy (Medtronic MiniMed) continuous (ON) **CONTROL**: Paradigm sensor-augmented pump therapy (Medtronic MiniMed) continuous (OFF)
Outcomes	**PRIMARY**: The primary end point was a comparison of the duration and severity of hypoglycemia measured with the YSI analyzer during successful LGS-On and LGS-Off sessions. **SECONDARY**: sensor accuracy, YSI glucose values at the end of the 4-h session, and the number of times sessions were terminated for YSI glucose values < 50 or > 300 mg/dL.
RESULTS	
Primary outcome:	• The mean $\pm$ SD hypoglycemia duration was less during LGS-On than during LGS-Off sessions (138.5 $\pm$ 76.68 vs. 170.7 $\pm$ 75.91 min, P = 0.006).
Secondary Outcomes	• During LGS-On compared with LGS-Off sessions, mean nadir YSI glucose was higher (59.5 $\pm$ 5.72 vs. 57.6 $\pm$ 5.69 mg/dL, P = 0.015), as was mean end-observation YSI glucose (91.4 $\pm$ 41.84 vs. 66.2 $\pm$ 13.48 mg/dL, P < 0.001). • Most (53.2%) end-observation YSI glucose values in LGS-On sessions were in the 70–180 mg/dL range, and none was > 250 mg/dL.
Stated conclusions	Results of this study provide evidence that the LGS feature, when programmed to suspend insulin delivery for 2 h when an SG value of $\leq$ 70 mg/dL is detected, can significantly reduce the duration and severity of hypoglycemia without causing significant rebound hyperglycemia.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic **PUBLICATION STATUS**: Peer review journal

Hermanides 2011[35]

Design	PARALLEL RANDOMIZED CONTROLLED CLINICAL TRIAL
Stated aim of study	”Therefore, we compared sensor-augmented pump therapy to intensive multiple daily injection therapy in patients with sub optimally controlled Type 1 diabetes mellitus in a randomized controlled multi-center trial.“
Participants	**WHO PARTICIPATED**: 83 adults, randomized to 44 in the CGM group and 39 in the control group. 78 patients completed the study **INSULIN PUMP USERS**: 0% **SEX**: CGM group 78% males, control 82% males **AGE** (mean years (SD)): CGM group 39.3 (11.9), control 37.3 (10.7) **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** (mean years (SD)): CGM group 16.9 (10.7), control 21. 0 (9.4) **INCLUSION CRITERIA**: age 18-65 years, type 1 diabetes at least one year, Hba1c ≥8.2% despite efforts to improve by re-education, including insulin pump therapy availability **EXCLUSION CRITERIA**: hearing or vision impairment or other chronic illnesses, pump treatment in the last 6 months **DIAGNOSTIC CRITERIA**: N/A. **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: continuous (6 months) **DURATION OF FOLLOW-UP**: 6 months **RUN-IN PERIOD**: 6 days **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 8 **COUNTRY**: Denmark, Switzerland, The Netherlands, Sweden, France, United Kingdom, Belgium, Italy **SETTING**: outpatients **CGMSYSTEM**: Paradigm sensor-augmented pump therapy (Medtronic MiniMed) continuous **CONTROL**: SMBG with 2 times 6 day blinded CGM measurement without subsequent treatment advice
Outcomes	**PRIMARY**: HbA1c **SECONDARY**: CGM derived time spent in hyperglycemia and hypoglycemia. Number of hypo- and hyperglycemic events per day. Sensor use. Proportion of patients reaching HbA1c <7%, contact time with study personnel, number of SMBG measurements per 3 weeks, insulin dose **ADDITIONAL**: Questionnaires: Health-related quality of life was assessed using the 36-item Short Form version 2. The Problem Areas in Diabetes Scale is a 20-item questionnaire that scores diabetes-related physiological distress. The Diabetes Treatment Satisfaction Questionnaire comprises six items and is scored on a 0-36 scale, with higher scores indicating higher satisfaction. The 13-item worry subscale of the Hypoglycemia Fear Survey was administered. The Hypoglycemia Fear Survey and the Problem Areas in Diabetes Scale could not be administered in all centers, because of lack of validated translations
RESULTS	
Primary outcome: HbA1c	• Mean HbA1c at baseline and at 26 weeks changed from 8.46% (sd 0.95) (69 mmol ⁄ mol) to 7.23% (sd 0.65) (56 mmol ⁄ mol) in the sensor-augmented insulin pump group and from 8.59% (sd 0.82) (70 mmol ⁄ mol) to 8.46% (sd 1.04) (69 mmol ⁄ mol) in the multiple daily injections group. • Mean difference in change in HbA1c after 26 weeks was -1.21% (95% confidence interval -1.52 to -0.90, P < 0.001) in favor of the sensor-augmented insulin pump group. • The proportion of patients reaching the European Association for the Study of Diabetes ⁄ American Diabetes Association HbA1c target of < 7% (53 mmol⁄ mol) was 34% in the

	sensor augmented insulin pump group and 0% in the multiple daily injection group (P < 0.001).
Secondary Outcomes	• No significant difference in change in percentage of time spent in hypoglycemia after 26 weeks was found between groups: 0.0% (95% confidence interval -1.6 to 1.7, P = 0.96). • The change in number of hyper- or hypoglycemic events did not differ between the groups. • The median total contact time during the trial was 240 min (interquartile range 195–353) in the multiple daily injection group and 690 min (interquartile range 526–1028) in the sensor augmented insulin pump group (P < 0.001). • The median contact time in the sensor-augmented insulin pump and multiple daily injection group before week 13 was 553 min (interquartile range 423–825) and 135 min (interquartile range 108–218), respectively (P = 0.001). • Between week 13 and the end of the trial, this was 75 min (interquartile range 60–120) in the sensor augmented insulin pump group and 60 min (interquartile range 40–75) in the multiple daily injection group (P = 0.001). • The mean sensor use in the sensor-augmented insulin pump group was 4.5 (sd 1.0) days ⁄ per week over the whole trial period and 79% of the patients using the sensor more than 60% of the time. • The Bolus Wizard was used by 86% of the sensor augmented insulin pump group patients at the end of the trial. • There was no evident relation between sensor use and HbA1c decrease within the sensor-augmented insulin pump group, when adjusted for baseline HbA1c, with a regression coefficient of 0.006 (P = 0.20).
Patient reported outcomes	• The difference in the Problem Areas in Diabetes score after 26 weeks, corrected for baseline scores, was significant at -7.9 (95% confidence interval -15.1 to -0.61, P = 0.03) in favor of the sensor-augmented insulin pump group. • The Diabetes Treatment Satisfaction Questionnaires and the Diabetes Treatment Satisfaction Questionnaire 'perceived frequency of hyperglycemia' scores improved significantly more in sensor augmented insulin pump group as compared with the multiple daily injection group. • For the 36-item Short Form version 2 questionnaire, only the change in the General Health and Social Functioning subscales differed significantly, both in favor of the sensor-augmented insulin pump group.
Adverse events	• There was a non-significant difference in the occurrence of severe hypoglycemia, with four episodes in the sensor-augmented insulin pump group (9%) and one episode in the multiple daily injection group (3%) (P = 0.21). • In total, seven serious adverse events were reported, of which two occurred in the sensor-augmented insulin pump group and five in the multiple daily injection group. • Only one serious adverse event was reported as being related to the device in the sensor augmented insulin pump group, where the patient was admitted to the hospital for ketoacidosis because of pump failure. • Other serious adverse events were: surgery for aorta bifurcation prosthesis, hemianopsia, respiratory tract infection, and ketoacidosis (x 2) in the multiple daily injection group and acute gastritis in the sensor-augmented insulin pump group. • Twenty patients reported 26 probable or possible device-related adverse events. Of these, 17 patients reported skin-related problems (itch ⁄exanthema ⁄infection ⁄ redness ⁄ plaster allergy ⁄bruising ⁄ hematoma) at the sensor or insulin infusion site.
Stated conclusions	Sensor augmented pump therapy effectively lowers HbA1c in patients with Type 1 diabetes sub optimally controlled with multiple daily injections.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic

	PUBLICATION STATUS: Peer review journal

Bukara-Radujkovic 2011[34]

Design	**PROSPECTIVE RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	Our study was conducted to analyze whether a three day use of CGMS can significantly contribute to therapeutic decisions and thus to glycemic control over and above information provided by the standardized blood glucose self –monitoring in young T1DM patients.
Participants	**WHO PARTICIPATED**: A total of 80 T1DM patients were randomly allocated into the experimental -CGMS (n=40) and self-monitored blood glucose – SMBG and the control only SMBG (n=40) group. **INSULIN PUMP USERS**: 0% **SEX**: CGM group 55% females, control 47.5% females **AGE** (mean years (SD)): CGM group 13.7 (3.3), control 11.8 (3.8) **ETHNIC GROUPS**: N/A. **DURATION OF DISEASE** (mean years (SD)): CGM group 6.3 (4.0), control 4.4 (2.7) **INCLUSION CRITERIA**: 1) HbA1c level ≥ 8%, 2) clinical diagnosis of insulin-dependent type 1 diabetes mellitus for at least 1 year, 3) patient's age 5 to 18 years, 4) availability for all office visits and compliance with the study protocol, and 5) compliance to wear a medical device for 72 consecutive hours. **EXCLUSION CRITERIA**: history of comorbidities, and noncompliance with the study protocol **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A. **DURATION OF INTERVENTION**: continuous 72 hours **DURATION OF FOLLOW-UP**: 6 months **RUN-IN PERIOD**: N/A. **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 1 **COUNTRY**: **Bosnia and Herzegovina** **SETTING**: outpatients **CGMSYSTEM**: Medtronic MiniMed, Northridge **CONTROL**: SMBG
Outcomes	HbA1c, average SMBG values and numbers of hypo- and hyperglycemic events.
RESULTS	
All outcomes:	• There was a significant improvement in HbA1c ($p < 0.001$), in both the experimental and the control group, without a significant difference between the groups. • Nevertheless, after 6 months the improvement of mean glycemic was noticed only in the experimental group. This finding was accompanied with a decrease in the number of hyperglycemic events and no increase in the number of hypoglycemic events in the experimental group.
Stated conclusions	The results suggest that the CGMS can be considered as a valuable tool in treating pediatric T1DM patients, however further research is needed to more accurately estimate to what extent, if any, it outperforms intensive self-monitoring of blood glucose.
Publication details	**LANGUAGE OF PUBLICATION**: English/ Bosnian **COMMERCIAL FUNDING**: Medtronic **PUBLICATION STATUS**: Peer review journal

Bergenstal (2010)[36] – STAR 3

Design	PARALLEL RANDOMIZED CONTROLLED CLINICAL TRIAL
Stated aim of study	"In this unmasked, randomized, controlled trial, called Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 3, we evaluated the use of sensor-augmented pump therapy and injection therapy at 30 diabetes centers in the United States and Canada for 1 year."
Participants	**WHO PARTICIPATED**: 485 patients, 329 adults and 156 children **SEX**: 274 males and 211 females **AGE** (mean age (SD)): Adults: 41.9 (12.3) in the CGM group and 40.6 (12.0) in the control group. Children: 11.7 (3.0) in the CGM group and 12.7 (3.1) in the control group **ETHNIC GROUPS**: 14 Hispanic, 443 white, 28 other **DURATION OF DISEASE** (mean years (SD)): Adults: 20.2 (12.2) in the CGM group and 20.2 (11.7) in the control group. Children: 4.7 (3.1) in the CGM group and 5.4 (3.7) in the control group **INCLUSION CRITERIA**: aged between 7 and 70 years, MDI for at least 3 months, HbA1c between 7.4 and 9.5%, under care for at least 6 months, access to a computer at home, history of SMBG average 4 times a day or more for the previous 30 days **EXCLUSION CRITERIA**: Use of insulin pump therapy within previous 3 years, history of at least two severe hypoglycemic events in the year before enrolment, use of pharmacologic non-insulin treatment for diabetes during the previous 3 months, pregnancy or intention to become pregnant **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: 12 months **DURATION OF FOLLOW-UP**: 12 months
Interventions	**STUDY CENTRES**: not reported **COUNTRY**: United States and Canada **SETTING**: outpatients **CGM SYSTEM**: MiniMed CGMS linked with Paradigm pump **CONTROL**: SMBG with MDI **TREATMENT BEFORE STUDY**: SMBG with MDI
Outcomes	**PRIMARY**: HbA1c **SECONDARY**: severe rates of hypoglycemia **ADDITIONAL**: N/A
RESULTS	
Primary outcome: HbA1c	• At 1 year, the baseline mean HbA1c level (8.3% in the two study groups) had decreased to 7.5% in the pump-therapy group (absolute reduction, 0.8±0.8 percentage points), as compared with 8.1% in the injection-therapy group (absolute reduction, 0.2±0.9 percentage points), for a between-group difference in the pump-therapy group of −0.6 percentage points (95% confidence interval [CI], −0.7 to −0.4; P<0.001) • Among adults, the absolute reduction in the mean HbA1c level was 1.0±0.7 percentage points in the pump-therapy group and 0.4±0.8 percentage points in the injection-therapy group, for a between-group difference in the pump-therapy group of −0.6 percentage points (95% CI, −0.8 to −0.4; P<0.001). • Among children, there was an absolute reduction in HbA1c of 0.4±0.9 percentage points in the pump-therapy group and an increase of 0.2±1.0 percentage points in the injection-therapy group, for a between-group difference favoring the pump-therapy group of −0.5 percentage points (95% CI, −0.8 to −0.2; P<0.001), with adjustment for the statistical model.
Secondary Outcomes	• Rates of severe hypoglycemia and diabetic ketoacidosis were similar in the two study groups and in the two age groups.

	• The area under the curve that was calculated from continuous glucose monitoring was similar in the two groups at 1 year for patients with hypoglycemia (defined either as <70 mg per deciliter [<3.9 mmol per liter] or as <50 mg per deciliter [<2.8 mmol per liter]) and was significantly lower in the pump-therapy group for patients with hyperglycemia (defined either as >180 mg per deciliter [>10.0 mmol per liter] or as >250 mg per deciliter [>13.9 mmol per liter])
Adverse Events	• There were two hospital admissions in the pump-therapy group for cellulitis related to insertion- site infections and one death from sudden cardiac arrest in a patient in the injection-therapy group who had a history of cardiovascular disease.
Stated Conclusions	In both adults and children with inadequately controlled type 1 diabetes, sensor augmented pump therapy resulted in significant improvement in glycated hemoglobin levels, as compared with injection therapy. A significantly greater proportion of both adults and children in the pump-therapy group than in the injection-therapy group reached the target glycated hemoglobin level.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Supported by Medtronic **PUBLICATION STATUS**: Peer review journal

Kordonouri [ONSET] 2010[37]

Design	**PARALLEL RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	"To assess the acceptance, efficacy and safety of the use of CGM in combination with insulin pump therapy from the diagnosis of type 1 diabetes in children and adolescents. Particularly, we set out to determine whether the use of sensor-augmented insulin pump therapy leads to better glycemic control, lower daily insulin requirements, higher residual beta cell function, lower incidence of severe hypoglycemia and better quality of life after 1 year of treatment compared with the use of a conventional insulin pump combined with conventional self-monitoring of blood glucose."
Participants	**WHO PARTICIPATED**: 160 patients with type 1 diabetes **SEX**: 80 females, 74 males **AGE** (mean age (SD)): 8.5 (4.6) in the CGM group, 9.1 (4.2) in the control group **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** (mean years (SD)): study started immediately after diagnosis **INCLUSION CRITERIA**: diagnosed with type 1 diabetes within 4 weeks of inclusion date, aged 1 through 16 years **EXCLUSION CRITERIA**: N/A **DIAGNOSTIC CRITERIA**: N/A. **CO-MORBIDITIES:** N/A. **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: 52 weeks **DURATION OF FOLLOW-UP**: 52 weeks **RUN-IN PERIOD**: no **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 5 centers **COUNTRY**: Pan-European **SETTING**: outpatients **CGM SYSTEM**: Medtronic Paradigm **CONTROL**: SMBG with CSII **TREATMENT BEFORE STUDY**: none
Outcomes	**PRIMARY**: HbA1c after 12 months **SECONDARY**: fasting C-peptide, glycemic variability, sensor usage, adverse events, children's

	health-related quality of life and parent's well being **ADDITIONAL**: N/A
RESULTS	
Primary Outcomes: HbA1c	• HbA1c of both treatment groups was not significantly different throughout the total period. At each follow-up visit, HbA1c levels in patients with sensor-augmented pump therapy were persistently below those of patients treated with insulin pump and SMBG • No significant differences between treatment groups were seen within the age groups. In total, 30 out of 76 patients (39.5%) with sensor-augmented pump had HbA1c levels below 7.0% at 12 months compared with 26 of 77 patients (33.8%) with insulin pump alone (p=0.464). • At 12 months, the 24 h glucose average was comparable between the groups (p=0.966), but glycemic variability was lower in the sensor group and reached statistical significance for MAGE (Mean amplitude of glycemic excursions).
Secondary Outcomes	• Patients with sensor-augmented insulin pumps performed fewer self-monitoring blood glucose finger sticks per day (5.2±2.0) than those with insulin pump alone (6.5±2.1, p<0.001). • At 12 months, the total daily insulin dose was 0.59±0.22 U/kg body weight in patients with sensor-augmented insulin pump and 0.64±0.23 U/kg body weight in those with insulin pump only (p=0.248). • Fasting C-peptide concentration at baseline was not associated with HbA1c (ρ=−0.099, r=0.225) and did not significantly differ between the groups • The proportion of patients with an increase in fasting C-peptide concentration from baseline to 12 months was 39.2% (29 of 74) in the sensor-augmented pump group and 34.2% (26 of 76) in the control group (p=0.528). • Significantly higher C-peptide concentrations were observed at 12 months in the sensor group • No episode of severe hypoglycemia was reported in patients with a sensor-augmented insulin pump compared with four episodes in patients with insulin pump alone (p=0.046). • The children's health-related quality of life showed significantly lower scores compared with European norm data (t values standardized: mean 50±10) for physical, psychological, social support, and school at baseline, normalizing after 6 months and remaining normal after 12 months with no difference between the intervention and control groups.
Stated Conclusions	"Sensor-augmented pump therapy starting from the diagnosis of type 1 diabetes can be associated with less decline in fasting C-peptide particularly in older children, although regular sensor use is a prerequisite for improved glycemic control."
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic Inc **PUBLICATION STATUS**: Peer review journal

O'Connell, 2009[38]

Design	**PARALLEL RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	"The aim of this study, therefore, was to assess the impact of patient led use of sensor guided pump management on indices of glycemic control in adolescents and young adults with type 1 diabetes and compare the impact with that of standard insulin pump therapy."
Participants	**WHO PARTICIPATED**: 62 patients with type 1 diabetes on CSII, randomized 1:1. 54 patients completed follow-up **INSULIN PUMP USERS**: 100% **SEX**: 29% males in each group **AGE** (mean age (SD)): 23.4 (8.6) in the CGM group, 23.0 (8.1) in the control group **ETHNIC GROUPS**: n.a.

	DURATION OF DISEASE (mean years (SD)): 11.1 (7.6) in the CGM group, 9.2 (7.2) in the control group **INCLUSIONCRITERIA**: age 13.0-40.0 years, type 1 diabetes for >1 year, use of insulin pump therapy including proficiency with use of a bolus-dose calculator for >3 months, HbA1c under or equal to 8.5%, reliably performing self-monitoring of blood glucose (SMBG) at least four times daily, and internet access. Willingness to use the subcutaneous sensor component of the system for at least 70% of the total 3 month study period was a further protocol requirement. **EXCLUSIONCRITERIA**: co-existent medical problems that would interfere with their ability to use the system (e.g. impaired vision), co-existent illness that otherwise predisposes to hypoglycemia (e.g. adrenal insufficiency) or a history of severe hypoglycemia while using insulin pump therapy **DIAGNOSTIC CRITERIA**: N/A. **CO-MORBIDITIES**: N/A **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: 3 months **DURATION OF FOLLOW UP**: 3 months
Interventions	**STUDY CENTRES**: 5 **COUNTRY**: Australia **SETTING**: outpatients **CGM SYSTEM**: Paradigm (Medtronic MiniMed) **CONTROL**: SMBG
Outcomes	**PRIMARY**: difference in the proportion of time in the target glycemic range during the 3 month study period (derived from CGM, target range 4-10 mmol/l) **SECONDARY**:HbA1c, time in hypoglycemic (below or equal to 3.9 mmol/l) and hyperglycemic (above or equal to 10.1 mmol/l) ranges and glycemic variability **ADDITIONAL**: N/A
RESULTS	
Primary Outcome:	• There was no difference between study groups in the primary outcome of proportion of time spent in the target glycemic range over 6 days of CGM at the end of the study. • In addition, no between-group difference was found in any of the outcomes of time spent hypo- or hyperglycemic or glycemic variation.
Secondary outcomes	• Despite the lack of difference in CGM- derived outcome variables, a significant effect on end-of-study HbA1c was evident between study groups. • End-of-study mean ± SD HbA1c was 7.1±0.8% in the intervention group vs 7.8± 0.8% in the control group, compared with baseline levels of 7.3±0.6% and 7.5±0.7%, respectively. • When adjusted for baseline values, mean HbA1c was 0.43% lower in the intervention group compared with that of the control group (95% CI 0.19 – 0.75%, p=0.009). • Overall, a reduction in HbA1c was achieved by 16/26 participants (64%) who used sensor-guided pump management compared with 5/29 participants (17%) who used standard pump therapy. HbA1c levels of <7% were also achieved more frequently in the intervention group. • HbA1c was 0.51% lower in participants who wore the sensor ≥70% of the total study period (95% CI 0.04–0.98%, p=0.04)
Adverse events	• No episodes of severe hypoglycemia or diabetic ketoacidosis occurred. • One participant in the intervention group was admitted to hospital for treatment of new-onset depression; the study protocol was completed nonetheless. • Mechanical problems arose: one participant in the intervention group experienced failure of her study insulin pump device necessitating use of her pre-study model until a replacement pump was delivered the following day. • It was also necessary to replace radiofrequency transmitters for four participants in the intervention group for whom these devices developed faults that precluded data storage

	(the problem was identified as repeated 'bad sensor' signals from insertion).
Stated Conclusions	In conclusion, this RCT has shown that patient-led use of sensor-guided pump management offers additional benefits for glycemic control when compared with standard insulin pump therapy regimens. Improvement in HbA1c in such a well-controlled cohort, despite no additional patient–clinician contact over the study period, is clinically significant and has encouraging implications for future use of this technology. Ongoing technological improvements and the introduction of algorithms to guide responses to RT-CGM data are likely to optimize use of this management tool.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic Inc **PUBLICATION STATUS**: Peer review journal

Newman [MITRE] 2009[39]

Design	**FOUR-ARM RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	The objective of this study was to evaluate whether the additional information provided by two minimally invasive glucose monitors resulted in improved glycemic control in people with poorly controlled insulin-requiring diabetes in both the long and medium term. In addition, the acceptability and health economic impact of the devices was assessed.
Participants	**WHO PARTICIPATED**: This was a four-arm randomized controlled trial. Two groups (groups 1 and 2) received minimally invasive glucose monitoring devices. Group 1 received the GlucoWatch Biographer device and group 2 the MiniMed Continuous Glucose Monitoring System (CGMS). These groups were compared with group 3, an attention control group that received standard treatment but with nurse feedback sessions at the same frequency as those in the groups receiving the devices, and group 4, a standard control group that reflected common practice in the clinical management of diabetes in the UK. **SEX**: (% male) GlucoWatch 56%; CGMS 56%; Attention control 54%; Standard care control 53% **AGE** (median (IQR)): GlucoWatch 55 (37–66; CGMS 53 (42–63); Attention control 53 (42–63; Standard care control 51 (42–59) **ETHNIC GROUPS**: (% white): GlucoWatch 87%; CGMS 91%; Attention control 90%; Standard care control 85% **DURATION OF DISEASE** (median (IQR)): GlucoWatch 16 (10.2–23.5); CGMS 15 (9–26); Attention control 18 (9–27); Standard care control 14 (9–24) **INCLUSION CRITERIA**: Individuals with insulin-treated diabetes mellitus receiving two or more injections daily [including continuous subcutaneous insulin infusion (CSII) pump users]; Age over 18 years; Duration of diabetes over 6 months; Fluent in English, Bengali, Cantonese or Turkish & HbA1c criteria **EXCLUSION CRITERIA**: Previous inability to use a capillary glucose meter; Previous use of the GlucoWatch or CGMS sensor; Presence of abnormal hemoglobin (presence of elevated levels of HbF or HbS); Pregnancy, or planned pregnancy in the next 18 months; Skin conditions, e.g. eczema, psoriasis or other skin irritation, at the sites of monitor use; Receiving dialysis; Visual or physical impairment limiting ability to use monitors; Planned major surgery (e.g. coronary artery bypass graft, hip replacement) within 3 months of consent; Participation in any other ongoing trial. **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: N/A. **DURATION OF INTERVENTION**: CGM daily **DURATION OF FOLLOW-UP**: 18 months **RUN-IN PERIOD**: unclear

	STUDY TERMINATED BEFORE REGULAR END: no
Interventions	**STUDY CENTRES**: 4 centers **COUNTRY**: UK **SETTING**: outpatients **CGM SYSTEM**: Medtronic Paradigm **CONTROL**: Glucowatch (active arm); Attention control & Standard care control
Outcomes	**PRIMARY**: Change in HbA1c from baseline to 18 months was the primary indicator of long-term efficacy in this study. **SECONDARY**: Change in HbA1c from baseline to 3 and 6 months evaluated short-term efficacy, and change from baseline to 12 months assessed efficacy in the medium term. Perceived acceptability of the GlucoWatch and CGMS was assessed by use and a self-report questionnaire, developed for the purpose of this study, at 3, 6, 12 and 18 months.
RESULTS	
Primary Outcome:	• At 18 months all groups demonstrated a decline in their HbA1c levels from baseline. Mean percentage changes in HbA1c were ‑1.4 for the GlucoWatch group, ‑4.2 for the CGMS group, ‑5.1 for the attention control group and ‑4.9 for the standard care control group.
Secondary outcomes	• A comparison between the devices in terms of use and acceptability indicated a decline in use of both devices but this was most marked in the GlucoWatch group, as opposed to the CGMS group, by 18 months (20% still using the GlucoWatch device versus 57% still using the CGMS). • The participants using the GlucoWatch device reported more side effects, greater interference with daily activities and more difficulty in using the device than those using the CGMS.
Stated Conclusions	*The outcomes indicate that continuous glucose monitors as assessed in this study do not lead to improved clinical outcomes in unselected individuals with poorly controlled insulin-requiring diabetes.*
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: No **PUBLICATION STATUS**: HTA

Raccah, 2009[40] - RealTrend study

Design	**PARALLEL RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	"In this trial we randomly initiated pump therapy in patients with insufficient metabolic control despite optimized basal-bolus injection regimens with either the MiniMed Paradigm REAL-Time insulin pump (PRT), an insulin pump that can receive and display CGM data from a separate subcutaneous glucose sensor, or conventional CSII, and compared glycemic outcomes after 6 months."
Participants	**WHO PARTICIPATE**D: 132 patients with type 1 diabetes, treated with MDI, randomized to insulin use by pump with integrated CGM (n=55) or pump + SMBG (n=60). 15 patients did not complete follow-up **INSULIN PUMP USERS**: 0% **SEX**: 54.5% males in the CGM group and 56.7% males in the control group **AGE** (mean age (SD)): 28.1 (15.1) in the CGM group, 28.8 (16.7) in the control group **ETHNIC GROUPS**: n.a. **DURATION OF DISEASE** (mean years (SD)): 11.2 (9.0) in the CGM group, 12.3 (8. 8) in the control group **INCLUSION CRITERIA**: age between 2 and 65 years, type 1 diabetes diagnosed for >12 months, follow-up by the respective investigator for at least 3 months, A1C ≥8%, and treatment with basal/bolus MDI with rapid insulin analogs at mealtimes. **EXCLUSION CRITERIA**: N/A

	DIAGNOSTIC CRITERIA: N/A **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: N/A. **DURATION OF INTERVENTION**: 6 months **DURATION OF FOLLOW-UP**: 6 months **RUN-IN PERIOD**: no **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 8 **COUNTRY**: France **SETTING**: outpatients **CGM SYSTEM**: Paradigm (Medtronic MiniMed) **CONTROL**: Insulin pump + SMBG
Outcomes	**PRIMARY**: HbA1c **SECONDARY**: mean glucose change and descriptive parameters for biochemical hyperglycemia (>190 mg/dl) and hypoglycemia (<70 mg/dl). Daily insulin use was also compared. **ADDITIONAL**: N/A.
RESULTS	
Primary Outcome: HbA1c	• HbA1c levels were significantly reduced in both groups (CGM: -0.81 + 1.09%, P < 0.001; CSII -0.57 + 0.94%, P < 0.001), but the difference in favor of the CGM group failed to reach statistical significance (P = 0.087). • Among patients who were fully compliant with the protocol, however, the reduction in HbA1c was significantly greater in the CGM group (CGM -0.96 + 0.93%, P < 0.001; CSII -0.55 + 0.93%, P < 0.001; intergroup comparison, P = 0.004)
Secondary Outcomes	• The mean glucose concentration decreased in both groups between baseline and study end. The reduction was significantly greater in the CGM group (-30.6 $\pm$ 54.0) than in the CSII group (-10.8 $\pm$ 39.6) (*P* = 0.005). • Significant differences in favor of the CGM group were also observed with respect to duration of hyperglycemic events, in the hyperglycemic area under the curve per day, in the mean amplitude of glycemic excursions (MAGE), and in overall SD of blood glucose values. • There was a significant increase in total daily doses (TDDs) of insulin between baseline and after 1 month of treatment in both the CGM group (ΔTDD = 5.8 $\pm$ 12.8 units) and the CSII group (ΔTDD = 2.2 $\pm$ 8.4 units, *P* = 0.032).
Adverse Events	• Ten serious adverse events were reported: three in the CGM group and seven in the CSII group. • Two episodes of ketoacidosis occurred in the CGM group when patients failed to react to the device's hyperglycemic alarms. • One episode of severe hypoglycemia with loss of consciousness also occurred in the CGM group. In this instance, the device was improperly calibrated, and acute alcohol intoxication may have played a role in the adverse event. • Three episodes of ketoacidosis occurred in the CSII group. • Four other serious adverse events occurred in the CSII group that were unrelated to the study devices or the protocol.
Stated Conclusions	CGM-enabled insulin pump therapy improves glycemia more than conventional pump therapy during the first 6 months of pump use in patients who wear CGM sensors at least 70% of the time.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic Inc **PUBLICATION STATUS**: Peer review journal

Hirsch 2008[41]

Design	PARALLEL RANDOMIZED CONTROLLED CLINICAL TRIAL
Stated aim of study	"The purpose of this was to assess the safety and clinical efficacy of a sensor-augmented insulin pump in adolescent and adult subjects."
Participants	**WHO PARTICIPATED**: 146 patients with type 1 diabetes, treated with insulin by pump, randomized to insulin pump with integrated CGM (n=72) or insulin pump + SMBG (n=74). 8 patients did not complete follow-up **INSULIN PUMP USERS**: 100% **SEX**: 78 females, 60 males **AGE** (mean age (SD)): 33.2 (16.39) years in the CGM group, 33.0 (14.60) years in the control group **ETHNIC GROUPS**: 2 Asian, 2 black, 10 Hispanic, 124 white. **DURATION OF DISEASE** (mean years (SD)): 16.7 (10.49) in the CGM group, 20.8 (12.41) years in the control group **INCLUSION CRITERIA**: between the ages of 12 and 72 years. A1C > 7.5%, and were diagnosed with type 1 diabetes > 1 year prior to entering the study. CSII for at least 6 months **EXCLUSION CRITERIA**: none **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: 26 weeks **DURATION OF FOLLOW-UP**: 26 weeks **RUN-IN PERIOD**: no **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 7 **COUNTRY**: USA **SETTING**: outpatients **CGM SYSTEM**: Paradigm (Medtronic MiniMed) **CONTROL**: Insulin pump + SMBG
Outcomes	**PRIMARY**: HbA1c **SECONDARY**: percentage of subjects achieving 7% HbA1c, hypoglycemia and hyperglycemia AUC and incidence. Safety **ADDITIONAL**: N/A.
RESULTS	
Primary outcome: HbA1c	• Change in HbA1c from baseline was significant for both groups (P <0.001), however, the between-group difference was not significant (P = 0.3706). • At Week 13, both groups showed a decrease in HbA1c values. At the end of study, the values increased, though not to baseline values. • Adult and adolescent subjects in both groups showed similar changes in HbA1c at 13 weeks and at the end of study. • Twenty (30.8%) SAP subjects achieved 7% HbA1c by Week 13 compared with eight (11.1%) SMBG subjects; the between-group difference was significant (P < 0.007). • At the end of study, 16 (24.2%) subjects in the SAP group reached the target HbA1c compared with 12 (19.4%) in the SMBG group; the between-group difference was not significant. • The number of SAP subjects who reached 7% HbA1c at either 13 weeks or the end of study was greater (P < 0.0031) compared with the SMBG subjects.
Secondary Outcomes	• **Sensor Compliance:** The effect of sensor compliance was significant (P = 0.0456); each 1 point (10%) increase in compliance was associated with a 41% increase in the probability of a 0.5% reduction in HbA1c • **Hyperglycemia AUC (>180 mg/dL):** Both study groups showed a significant (P = 0.0001)

	decrease in mean values at the end of study (SMBG, –9.7 ± 16.5 mg/dL/min; SAP, –11.3 + 19.3 mg/dL/min, P = 0.0001). • **Hyperglycemia incidence:** Mean numbers of hyperglycemic events per patient per day (>180 mg/dL) at baseline for SMBG and SAP subjects were 2.667 ± 0.649 and 2.635 ± 0.635, respectively. • **Hypoglycemia AUC (<70 mg/dL):** Overall, there was no change in mean hypoglycemia AUC in the SAP group, whereas mean values in the SMBG group increased significantly (P = 0.001). • **Hypoglycemia incidence***:* Mean numbers of hypoglycemic events at baseline for SMBG and SAP subjects were 0.8348 ± 0.728 and 0.8378 ± 0.725, respectively. The number of hypoglycemic events (<70 mg/ dL) in SMBG subjects increased significantly (*P* = 0.0008) to 1.1663 ± 0.744 at the end of study compared to SAP subjects (0.8828 ± 0.756; *P* = 0.6154).
Adverse Events	• Seventeen serious adverse events occurred. One patient experienced a skin abscess (twice) at the insulin infusion site, and one patient in the SAP group experienced diabetic ketoacidosis. The remaining 14 were severe hypoglycemia events. • Of the 14 events of severe hypoglycemia; 11 events occurred in the SAP group. Comparison between groups revealed a statistical significance of P = 0.04. • The 11 severe hypoglycemia episodes in the SAP occurred in eight subjects. Six of these events were deemed to be not related or unlikely to be related to the device. For example, subjects were not wearing the device or not using the device. In the remaining five instances where the severe hypoglycemic episodes were thought to be possibly related to the device, the Safety Review Board established the following facts: subjects ignored the alerts (i.e., subject did not respond to alarms that warned of low sensor readings); subjects tended to inject multiple boluses of insulin without using the Bolus Wizard, resulting in stacking; or subjects "blind bolused" (i.e., based treatment decisions on sensor reading only, without confirming with a blood glucose test).
Stated Conclusions	CGM-enabled insulin pump therapy improves glycemic more than conventional pump therapy during the first 6 months of pump use in patients who wear CGM sensors at least 70% of the time.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic Inc **PUBLICATION STATUS**: Peer review journal

Murphy 2008[43]

Design	**PROSPECTIVE, OPEN-LABEL RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	To evaluate the effectiveness of continuous glucose monitoring during pregnancy on maternal glycemic control, infant birth weight, and risk of macrosomia in women with type 1 and type 2 diabetes.
Participants	**WHO PARTICIPATED**: 71 women with type 1 diabetes (n=46) or type2 diabetes (n=25) allocated to antenatal care plus continuous glucose monitoring (n=38) or to standard antenatal care (n=33). **INSULIN PUMP USERS**: N/A **SEX**: 100% pregnant females **AGE** (mean age (SD)): CGM: 30.2 (6.3); standard antenatal care 32.5 (5.9) **ETHNIC GROUPS**: (% white) CGM: 89%; standard antenatal care 88% **DURATION OF DISEASE** (mean years (SD)): CGM: 15.2 (11.0); standard antenatal care 10.0 (8.8) **INCLUSION CRITERIA**: pregnant women aged 16-45 with type 1 and type 2 diabetes if they provided written informed consent and were willing to wear a continuous glucose monitor. **EXCLUSION CRITERIA**: Exclusion criteria were limited to severe medical or psychological comorbidity, and no women were excluded.

	DIAGNOSTIC CRITERIA: N/A. **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: N/A. **DURATION OF INTERVENTION**: 5-7 days **DURATION OF FOLLOW-UP**: after delivery **RUN-IN PERIOD**: unclear **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 2 **COUNTRY**:UK **SETTING**: outpatients **CGM SYSTEM**: CGMS Gold Medtronic- MiniMed, Northridge, USA **CONTROL**: standard antenatal care
Outcomes	**PRIMARY**: The primary outcome was maternal glycemic control during the second and third trimesters from measurements of HbA1c levels every four weeks. **SECONDARY**: Secondary outcomes were birth weight and risk of macrosomia using birth weight standard deviation scores and customized birth weight centiles.
RESULTS	
Primary Outcome:	• Although theHbA1c level was consistently lower in the intervention arm no statistical difference was found mean levels between the two groups at booking or throughout the first two trimesters. • Differences between the two arms began to emerge between 28 and 32 weeks' gestation: mean HbA1c levels in the intervention arm were 6.1% (SD 0.6) compared with 6.4% (SD 0.8) in the control arm, with a trend towards but not reaching statistical significance (P=0.1). • In later pregnancy, at 32-36 weeks' gestation, a further reduction in HbA1c levels was seen in the intervention arm but no further reductions in the control arm—a difference in mean HbA1c levels of 0.6% between groups: 5.8% (SD 0.6) in intervention arm compared with 6.4% (SD 0.7) in control arm (P=0.007).
Secondary outcomes	• From 71 pregnancies there were 69 living infants • Compared with healthy singletons of women in the control group (n=30), those of women in the intervention group (n=32) had decreased mean birth weight standard deviation scores (0.9 v 1.6; effect size 0.7 SD, 95% confidence interval 0.0 to 1.3; P=0.05). • No skin infections occurred although mild erythema and inflammation were often seen around the insertion site of the sensor. • Two pregnancies in intervention women ended prematurely (one miscarriage and one termination).
Stated Conclusions	Continuous glucose monitoring during pregnancy is associated with improved glycemic control in the third trimester, lower birth weight, and reduced risk of macrosomia.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: Medtronic donated CGM systems **PUBLICATION STATUS**: Peer review journal

Yoo 2008[42]

Design	**PROSPECTIVE, OPEN-LABEL RANDOMIZED CONTROLLED CLINICAL TRIAL**
Stated aim of study	The purpose of this study was to determine whether a RTCGM in the home setting is useful for poorly controlled type 2 diabetes with a view to modify a patient's diet and exercise habits and improve disease self-control efforts, thereby inducing better glycemic control compared with SMBG.
Participants	**WHO PARTICIPATED**: 65 patients with poorly controlled type 2 diabetes allocated to rt-CGM (n=32) or control with SMBG (n=33) **INSULIN PUMP USERS**: N/A.

	SEX: (% male): rt-CGM (34.5%); SMBG (50%) **AGE** (mean age (SD)): rt-CGM: 54.6 (6.8); SMBG 57.5 (9.0) **ETHNIC GROUPS**: N/A **DURATION OF DISEASE** (mean years (SD)): rt-CGM: 11.7 (5.8); SMBG: 13.3 (4.9) **INCLUSION CRITERIA**: (1) 20–80 years of age, (2) type 2 diabetes with use of oral hypoglycemic agents (OHA) or insulin for at least 1 year, (3) HbA1c between 8.0% and 10%, (4) a stable insulin or OHA regimen for the prior 2 months, and (5) a stable dose of antihypertensive or lipid-lowering drugs for at least 4 weeks. **EXCLUSION CRITERIA**: (1) severe diabetic complications (e.g., diabetic foot or severe diabetic retinopathy), (2) corticosteroid use in the previous 3 months, (3) liver disease (aspartate aminotransferase or alanine aminotransferase levels >2.5 times the reference level), (4) renal insufficiency with a serum creatinine level $\geq$2.0 mg/dL, and (5) other medical problems that affected study results or trial participation. **DIAGNOSTIC CRITERIA**: N/A **CO-MORBIDITIES**: N/A. **CO-MEDICATION**: N/A **DURATION OF INTERVENTION**: 3 days **DURATION OF FOLLOW-UP**: 3 months **RUN-IN PERIOD**: unclear **STUDY TERMINATED BEFORE REGULAR END**: no
Interventions	**STUDY CENTRES**: 4 **COUNTRY**: Korea **SETTING**: outpatients **CGM SYSTEM**: Guardian RT (Medtronic, USA) **CONTROL**: SMBG
Outcomes	**PRIMARY**: the difference in the change inHbA1c levels after 3months between the Guardian RT and SMBG groups. **SECONDARY**: Other variables were fasting blood glucose, postprandial 2 h blood glucose, lipid profiles, weight, waist circumference, and body mass index (BMI).
RESULTS	
Primary Outcome:	• The Guardian RT group had a significant reduction in the HbA1c level after 12 weeks later (9.1 $\pm$ 1.0% to 8.0 $\pm$ 1.2%, P < 0.001). • There was also a significant reduction of HbA1c level in the SMBG group (8.7 $\pm$ 0.7% to 8.3 $\pm$ 1.1%, P = 0.01). • Moreover, a significant difference in the amounts of improvement in the HbA1c level existed between the two groups (P = 0.004)
Secondary outcomes	• The proportion of time the blood glucose level was between 80 and 250 mg/dL which was considered the relatively well-controlled range, increased from 61.6% to 71.6%, but this was not statistically significant (P = 0.07). • The time spent in the hypoglycemic range (<60 mg/ dL) was mildly increased, although there was no statistical significance (P = 0.10) and there were no reports of clinically symptomatic hypoglycemic events during the study period • In the RT-CGM group, there was a significant reduction in total daily calorie intake, weight, body mass index (BMI), and postprandial glucose level, and a significant increase in total exercise time per week after 3 months.
Stated Conclusions	In conclusion, we have demonstrated that the Guardian RT continuous glucose monitoring system was useful in the outpatient setting for poorly controlled type 2 diabetes with the goal to modify a patient's diet and exercise habits and improve self-control of disease efforts, thereby inducing better glycemic control, compared with SMBG.
Publication details	**LANGUAGE OF PUBLICATION**: English **COMMERCIAL FUNDING**: No **PUBLICATION STATUS**: Peer review journal

Appendix E: Literature Searches

The Embase, Medline, PubMed, Cochrane Library –HTA and Cochrane reviews databases were the primary databases searched in this submission. **Table 27** outlines the time periods/dates covered for each electronic database searched. The Embase and Medline databases were searched simultaneously through the Embase.com portal. All searches of primary databases were run on the **1st of March 2017.** After applying the PICO and exclusion criteria 37 unique citations were included in this submission. See the Prisma flow chart for evidence selection in **Figure 2**.

Table 27 Number of citations retrieved from **each primary database**

	Date searched	**Total citations retrieved**	**Total after duplicates removed**
Embase/Medline	March 1st 2017	862	1264
PubMed		687	
Cochrane reviews/HTA		26	
TOTAL		**1575**	

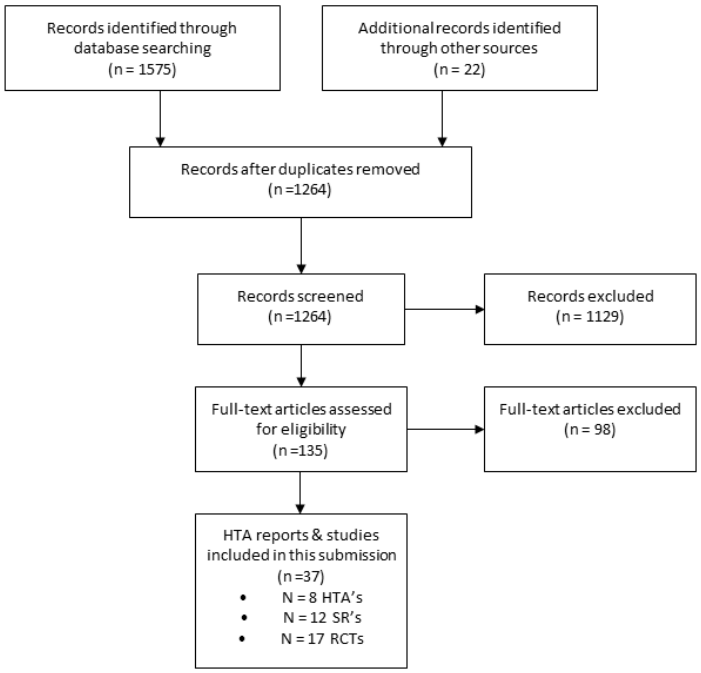

Figure 2 Prisma flow chart for selection of included evidence

Table 28 Embase Search strategy

	EMBASE SEARCH 1st March 2017	HITS
#2	'insulin dependent diabetes mellitus'/exp	95912
#3	diabetic ketoacidosis'/exp OR 'diabetic ketoacidosis'	10717
#4	'type 1 diabetes'	46867
#5	iddm OR t1dm OR t1d	21743
#6	hba1c OR hb AND a1 OR hba1 OR a1c	79839
#10	non insulin dependent diabetes mellitus'	190669
#11	niddm OR t2dm OR t2d	39688
#12	adult-onset diabetes mellitus'	182
#13	type ii diabetes mellitus'	3426
#14	'type ii diabetes'	10495
#15	maturity-onset diabetes'	2161
#18	pregnancy diabetes mellitus'/exp	26831
#19	gestational diabetes'	16133
#20	pregnancy induced' NEAR/3 'diabetes mellitus'	94
#22	gdm	7621
#25	'continuous glucose monitoring system'	1088
#26	diabetes AND cgm	2341
#27	diabetes AND cgms	1023
#29	'sensor augmented pump'	322
#42	'diabetes mellitus'/exp	774205
#86	'randomized controlled trial'/exp	433209
#87	'randomization'	90484
#88	'single blind procedure'	25592
#89	'double blind procedure'	135423
#90	random* NEAR/2 allocation	2834
#91	'prospective study'	415136
#92	'controlled study'	5283581
#95	rct	26193
#97	'systematic review'	170591
#98	'meta analysis'	181295
#99	metaanalysis*.ab,ti.	0
#100	'biomedical technology assessment'/exp	11746
#101	'technology assessment'	24900
#107	'continuous glucose monitoring':ti,ab	4160
#108	'continuous glucose monitoring system':ti,ab	971
#109	cgm:ti,ab	2737

#110	cgms:ti,ab	1076
#111	diabetes	905087
#112	#42 OR #111	944539
#113	#109 OR #110	3624
#114	#112 AND #113	3056
#124	#2 OR #3 OR #4 OR #5 OR #6 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #18 OR #19 OR #20 OR #22	341681
#126	#86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #95 OR #97 OR #98 OR #99 OR #100 OR #101	5921581
#130	#25 OR #26 OR #27 OR #29 OR #107 OR #108 OR #114	5162
131	#124 AND #126 AND #130	1247
133	#131 AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py) AND ('article'/it OR 'review'/it) AND [humans]/lim	862

Table 29 Pubmed Search strategy

PUBMED search	HITS
Search ((((((((((("Randomized Controlled Trial" [Publication Type]) OR randomization) OR single blind study) OR double blind study) OR controlled trial) OR rct study) OR "Meta-Analysis" [Publication Type]) OR systematic review) OR health technology assessment) OR hta assessment)) AND ((((((((((continuous glucose monitoring) OR continuous glucose monitoring system) OR (diabetes AND cgm)) OR (diabetes AND cgms)) OR sensor augmented pump) OR minimed) OR paradigm veo) OR (smartguard AND diabetes)) OR (enlite AND diabetes)) OR (ipro AND diabetes)) OR artificial pancreas diabetes)) AND ((((((((((("Diabetes Mellitus, Type 1"[Mesh]) OR type 1 diabetes) OR diabetes type 1) OR iddm) OR (iddm OR t1dm OR t1d)) OR diabetic ketoacidosis) OR (hba1c OR hba1 OR a1c))) OR (((((("Diabetes Mellitus, Type 2"[Mesh]) OR (t2dm OR t2d)) OR adult onset diabetes) OR type ii diabetes mellitus) OR maturity-onset diabetes)) OR ((((("Pregnancy in Diabetics"[Mesh]) OR gestational diabetes) OR gestational diabetes mellitus) OR pregnancy induced near/3 diabetes mellitus)) Sort by: PublicationDate Filters: Publication date from 2005/01/01 to 2017/12/31; Humans	**687**

Table 30 Cochrane Library Search strategy

1	continuous glucose monitor	83
2	cgm and diabetes	377
3	cgms and diabetes	129
4	sensor augmented pump	123
5	artificial pancreas	140
6	(#2 or #5) and diabetes	493
7	#1 or #2 or #3 or #6	642
	HTA Database results	**15**
	Cochrane reviews retrieved	**11**

Appendix F: Questionnaires & PRO measures

MITRE Skin Scale

Problems

0 = none

1 = fitting device

2 = calibration

3 = inaccurate results

4 = inaccurate alarm

5 = other (please comment)

Redness

0 = none

1 = mild, patchy red spots

2 = moderate/noticeable spots

3 = intense within site

4 = intense with flaring beyond site

Swelling

0 = no problem

1 = mild lumpiness

2 = moderate lumpiness

3 = severe lumps

4 = blisters

Total

ADD Redness score to Swelling score. If greater than or equal to 6, call nurse

Irritation

0 = none

1 = mild

2 = moderate

3 = severe

Appendix G: Reference list

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Appendix H: Supporting Documents

MINIMED™ 670G SYSTEM

PUBLISHED & REAL-WORLD DATA REPORT

September 25, 2017

CONTENTS

ABBREVIATIONS

ADA	American Diabetes Association	**LGS**	Low Glucose Suspend
CGM	Continuous Glucose Monitoring	**MDI**	Multiple Daily Injections
CSII	Continuous Subcutaneous Insulin Infusion	**SAP**	Sensor Augmented Pump
DKA	Diabetic Ketoacidosis	**SMBG**	Self-Monitoring of Blood Glucose
DM	Diabetes Mellitus	**T1DM**	Type 1 Diabetes Mellitus
A1C	Glycated Hemoglobin	**T2DM**	Type 2 Diabetes Mellitus

940M17153-011 24SEP2017

SUMMARY

The purpose of this summary is to review published clinical data and unpublished real-world data from voluntary uploads of MiniMed™ 670G system to CareLink™ Personal database to describe the value of insulin pump therapy as a proven safe therapy for the treatment of type 1 insulin dependent diabetes mellitus in patients 14 years and older.

BACKGROUND

- Controlling blood sugar (glucose) levels is the major goal of diabetes treatment, in order to prevent complications of the disease. Type 1 diabetes is managed with insulin as well as dietary changes and exercise.

- Insulin pump therapy, also known as continuous subcutaneous insulin infusion (CSII), is an important and evolving form of insulin delivery. The aim of CSII is to provide a flexible method for administering insulin, which tries to mimic the body's natural pattern of a small amount of insulin being present in the body all the time (basal infusion) and peaks of insulin release in response to meals (boluses).

- Continuous glucose monitoring (CGM) devices continuously monitor and record interstitial fluid glucose levels.

- A sensor-augmented insulin pump (SAP) combines the technology of an insulin pump with a continuous glucose monitoring sensor that transmits sensor glucose readings to the insulin pump.

MINIMED 670G SYSTEM

- The MiniMed 670G system is the latest insulin pump developed by Medtronic and is an iterative improvement on the previous sensor augmented pumps, such as the MiniMed 530G system and MiniMed 630G system.
- The MiniMed 530G and 630G systems (approved in US) and MiniMed 640G system (not approved in the US) were designed to reduce low glucose excursions by suspending insulin delivery when a patient's glucose level drops below a preset threshold.[1-2]
- **The MiniMed 670G system goes a step further than the earlier versions by using an algorithm to help keep sensor glucose levels within a target.**
- The two key features of the MiniMed 670G system that address unmet needs include:
    - Adjusts basal insulin delivery based on sensor glucose values
    - Ability to personalize insulin delivery (Auto Mode, Suspend before low, and Suspend on low function)

MINIMED 670G SYSTEM: PUBLISHED CLINICAL DATA AND POSTERS

Table 1 below lists the studies and posters presented on the MiniMed 670G system during 2016 and 2017.

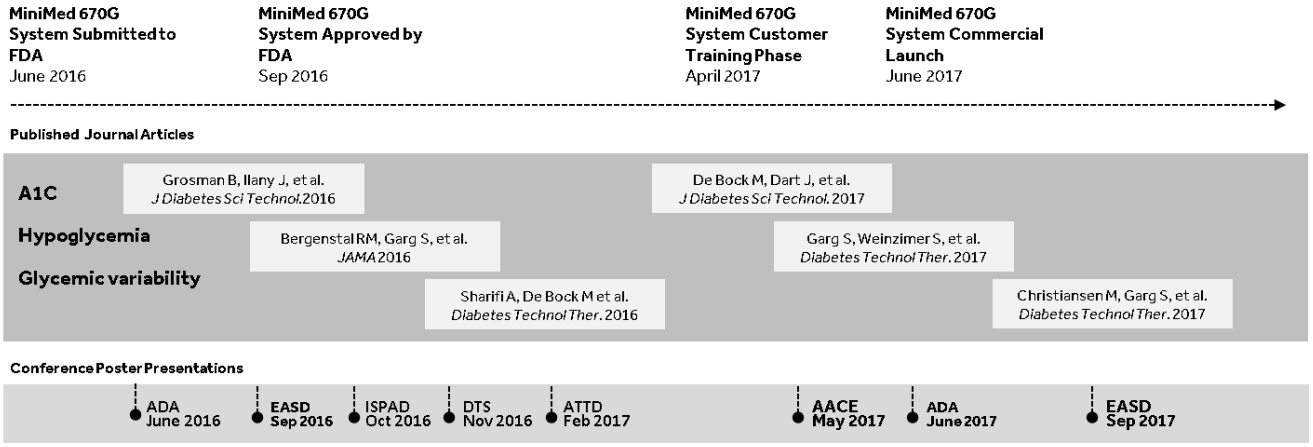


Table 1: *Publication timeline and poster presentations*

GROSMAN (FEBRUARY 2016)[3]

An efficacy and safety study of the Medtronic Hybrid Closed-Loop (HCL) system (SAP in communication with a control algorithm housed on an Android-based cellular device algorithm) was tested in subjects with type 1 diabetes.

Nine subjects with type 1 diabetes (5 female, mean age 53.3 years, mean A1C 7.2%) underwent 9 studies totaling 571 hours of closed-loop control using either default or personalized parameters. The system required meal announcements with estimates of carbohydrate (CHO) intake that were based on metabolic kitchen quantification (MK), dietician estimates (D), or subject estimates (Control). Postprandial glycemia was compared for MK, D, and Control meals.

The overall sensor glucose mean was 145 ± 43mg/dL, the overall percentage time in the range 70-180 mg/dL was 80%, the overall percentage time <70 mg/dL was 0.79%. Compared to intervals of default parameter use (225 hours), intervals of personalized parameter use (346 hours), sensor glucose mean was 158 ± 49 mg/dL and 137 ± 37 mg/dL (P < .001), respectively, and included more time in range (87% vs 68%) and less time below range (0.54% vs 1.18%). Most subjects underestimated the CHO content of meals, but postprandial glycemia was not significantly different between MK and matched Control meals (P = .16) or between D and matched Control meals (P = .76). There were no episodes of severe hypoglycemia.

Conclusion: The HCL system was efficacious and safe during this study. Personally adapted HCL parameters were associated with more time in range and less time below range than default parameters. Accurate estimates of meal carbohydrate did not contribute to improved postprandial glycemia.

BERGENSTAL (SEPTEMBER 2016)[4]

The pivotal study for the **MiniMed 670G system** conducted in 124 patients aged 14 to 75 years (mean age, 37.8years [SD, 16.5]; men, 44.4%) with type 1 diabetes for at least 2 years, and A1C less than 10%. This study was conducted in 10 centers (9 in the United States, 1 in Israel) between June 2, 2015, and November 11, 2015.

The MiniMed 670G system automatically adjusts basal insulin delivery based on subcutaneous sensor data. This before and after study had a two-week run-in period (baseline) for patients to learn the device without the automated features followed by a three-month study period.

Conclusion: Over 12,389 patient-days, no episodes of severe hypoglycemia or ketoacidosis were observed. Glycated hemoglobin levels changed from7.4% (SD,0.9) at baseline to 6.9% (SD, 0.6) at study end (0.5% improvement). Time with sensor glucose levels between 51mg/dL and 70mg/dL reduced by 44%; and 72.2% of the time was spent in correct target glucose range of 71-180 mg/dL.

SHARIFI (DECEMBER 2016) [5]

The objective of the study was to compare glycemia, treatment satisfaction, sleep quality, and cognition using a nighttime Android-based hybrid closed-loop system (Android-HCLS) with sensor-augmented pump with low-glucose suspend function (SAP-LGS) in people with type 1 diabetes.

An open-label, prospective, randomized crossover study of 16 adults (mean [SD] age 42.1 [9.6] years) and 12 adolescents (15.2 [1.6] years) was conducted. The primary outcome studied was the percent continuous glucose monitoring (CGM) time (00:00– 08:00 h) within target range (72–144 mg/dL). The secondary endpoints were percent CGM time above target (>144 mg/dL); below target (<72 mg/dL); glycemic variability; symptomatic hypoglycemia; adult treatment satisfaction; sleep quality; and cognitive function.

The primary outcome for all participants was not statistically different between Android-HCLS and SAP-LGS (mean [SD] 59.4 [17.9]% vs. 53.1 [18]%; p = 0.14). Adults had greater percent time within target range with Android-HCLS vs. SAP-LGS (57.7 [18.6]% vs. 44.5 [14.5]%; p < 0.006); less time above target (42.0 [18.7]% vs. 52.6 [16.5]%; p = 0.034); lower glycemic variability (35 [10.7] mg/dL vs. 46 [10.7] mg/dL; p = 0.003); and less (median [IQR]) time below target (0.0 [0.0–0.4]% vs. 0.80 [0.0–3.9]%; p = 0.025). In adolescents, time below target was lower with Android-HCLS vs. SAP-LGS (0.0 [0.0–0.0]% vs. 1.8 [0.1–7.9]%; p = 0.011). Number of nocturnal symptomatic hypoglycemic episode were less (1 vs. 10; p = 0.007) in adolescents, but not adults (5 vs. 13; p = 0.059). In adults, treatment satisfaction increased by 10 points (p < 0.02). Sleep quality and cognition did not differ.

Conclusion: Android-HCLS in both adults and adolescents reduced nocturnal hypoglycemia and, in adults, improved overnight time in target range and treatment satisfaction compared with SAP-LGS.

DE BOCK (JANUARY 2017) [6]

The aim of this observational study was to test whether an algorithm that includes a limit to insulin delivery is effective at protecting against hypoglycemia under those circumstances.

This study was designed to observe 8 participants with type 1 diabetes, where a hybrid closed loop system (HCL) (Medtronic™ 670G system) was challenged with hypoglycemic stimuli: exercise and an overreading glucose sensor.

There was no overnight or exercise-induced hypoglycemia during HCL insulin delivery. All daytime hypoglycemia was attributable to postmeal bolused insulin in those participants with a more aggressive carbohydrate factor.

Conclusion: HCL systems rely on accurate carbohydrate ratios and carbohydrate counting to avoid hypoglycemia. The algorithm that was tested against moderate exercise and an overreading glucose sensor performed well in terms of hypoglycemia avoidance. Algorithm refinement continues in preparation for long-term outpatient trials.

GARG (MARCH 2017) [7]

The safety and effectiveness of the in-home use of a hybrid closed-loop (HCL) system that automatically increases, decreases, and suspends insulin delivery in response to continuous glucose monitoring were investigated on 30 adolescents (ages 14–21 years) and 94 adults (ages 22–75 years) with type 1 diabetes in a multicenter (nine sites in the United States, one site in Israel) pivotal trial[4] (*Bergenstal, September 2016*).

The Medtronic MiniMed 670G system was used during a 2-week run-in phase with Manual Mode and, thereafter, with Auto Mode enabled during a 3-month study phase.

For adolescents (mean – standard deviation [SD] 16.5 ±2.29 years of age and 7.7 ± 4.15 years of diabetes) used the system for a median 75.8% (interquartile range [IQR] 68.0%±88.4%) of the time (2977 patient-days). For adults (mean – SD 44.6 ± 12.79 years of age and 26.4 ± 12.43 years of diabetes) used the system for a median 88.0% (IQR 77.6%±92.7%) of the time (9412 patient-days). From baseline run-in to the end of study phase, adolescent and adult A1C levels decreased from 7.7% ± 0.8% to 7.1% ± 0.6% (P < 0.001) and from 7.3% ± 0.9% to 6.8% ±0.6% (P < 0.001, Wilcoxon signed-rank test), respectively. The proportion of overall in-target (71–180

mg/dL) sensor glucose (SG) values increased from 60.4% ± 10.9% to 67.2% ± 8.2% (P < 0.001) in adolescents and from 68.8% ±11.9% to 73.8% ± 8.4% (P < 0.001) in adults. There were no severe hypoglycemic or diabetic ketoacidosis events.

Conclusions: HCL therapy was safe during in-home use by adolescents and adults and the study phase demonstrated increased time in target, and reductions in A1C, hyperglycemia and hypoglycemia, compared to baseline.

CHRISTIANSEN (JULY 2017) [8]
This study evaluated the accuracy and performance of a fourth-generation subcutaneous glucose sensor (Guardian™ Sensor (3)) in the abdomen and arm.

In this study, 88 subjects (14–75 years of age, mean – standard deviation [SD] of 42.0 ± 19.1 years) with type 1 or type 2 diabetes participated in the study. Subjects wore two sensors in the abdomen that were paired with either a MiniMed 640G insulin pump (not approved in the U.S.), or an iPhone® or iPod® touch running a glucose monitoring mobile application (Guardian™ Connect system*) and a third sensor in the arm, which was connected to a glucose sensor recorder (GSR -not approved in the U.S.).

The overall mean absolute relative difference (MARD– SD) between abdomen sensor glucose (SG) and YSI reference values was 9.6% ±9.0% and 9.4% ± 9.8% for the MiniMed 640G (not approved in the U.S.) insulin pump and Guardian Connect system (not approved in the U.S.), respectively; and 8.7% ± 8.0% between arm SG and YSI reference values. The percentage of SG values within 20% agreement of the YSI reference value (for YSI >80 mg/dL) was 90.7% with the MiniMed 640G (not approved in the U.S.) insulin pump, 91.8% with the Guardian Connect (not approved in the U.S.) system, and 93.1% for GSR-connected arm sensors (not approved in the U.S.). Mean functional sensor life, when calibrating 3–4 times/day, was 145.9 ± 39.3 hours for sensors paired with the MiniMed 640G (not approved in the U.S.) insulin pump, 146.1 ± 41.6 hours for sensors paired with the Guardian Connect system (not approved in the U.S.), and 147.6 ±40.4 hours for sensors connected to the GSR (not approved in the U.S.). Responses to survey questions regarding sensor comfort and ease of use were favorable.

Conclusions: The Guardian Sensor (3) glucose sensor*, whether located in abdomen or the arm, provided accurate glucose readings when compared with the YSI reference and demonstrated functional life commensurate with the intended 7-day use.

***** The Guardian Sensor (3) is only approved for use in the abdomen with the MiniMed 670G system

2016 – 2017 POSTERS PRESENTED AT CONFERENCES

Title	Conference	Conclusions
Pivotal Trial Of A Hybrid Closed-Loop System In Type 1 Diabetes	ADA 2016	Hybrid closed-loop insulin delivery can help patients reduce hypo- and hyperglycemia and safely achieve ADA recommended A1C goals. This study suggests that the Medtronic MiniMed HCL system should be considered for non-investigational use in adults and adolescents with type 1 diabetes in the home setting.
Performance Of A Fourth-Generation Glucose Sensor During A Pivotal Hybrid Closed-Loop (HCL) Trial	EASD 2016	The accuracy of the sensor was verified with the i-STAT blood glucose reference used during the Hotel Stay, and aligned with sensor glucose values during the Study Phase of the Hybrid Closed-Loop Pivotal Trial. The performance of the sensor in the Hybrid Closed-Loop Pivotal Trial was consistent with that determined in the Fourth-Generation Sensor Study. These results support the use of the fourth-generation glucose sensor in the automated control of insulin delivery with the Hybrid Closed-Loop System.
Evaluation Of Night Time Glucose And Insulin During A Pivotal Hybrid Closed Loop Trial In Type-1 Diabetes	DTS 2016	The MiniMed 670G system improves nighttime in target range, for adolescents and adults, similar to overall time in range. While overall TDD increased, there was no significant difference in nighttime insulin delivered, between run-in and study phase. Improved nighttime glucose control appears to be related to the ability of the HCL system to dynamically adjust insulin delivery based on sensor glucose.
In-Silico Performance Of 670G Hybrid Closed Loop (HCL) With Cumulative Error In Meter BG And Sensor Measurements	DTS 2016	Medtronic's 670G HCL system demonstrated safety in improbable scenarios with no severe hypoglycemia <50 mg/dL and limited time in severe hyperglycemia >300 mg/dL
Role Of Appropriate Pre-Meal Insulin Bolus On The Hybrid Closed Loop System-MiniMed™ 670G	ADA 2017	Analysis of a subgroup of subjects in the HCL pivotal trial indicates a significant effect of aggressive carb-insulin ratio on daytime glucose. Aggressiveness of the meal bolus had no effect on glucose at wake-up time. Overall, the system is proven to be safe and demonstrates a positive effect of automating insulin delivery.
Maintaining Glucose Control At One + Year Of MiniMed™ 670G System Home Use; Single Center Experience	ADA 2017	At this single-center, the improvement in A1C and reduction in hypoglycemic and hyperglycemic excursions, were sustained at one year of MiniMed 670G home use.

Glycemic Outcomes In Subjects With And Without Prior CGM Experience, In The MiniMed™ 670G System Pivotal Trial	EASD 2017	Improved glycemic control (i.e., reduced A1C, within-day SG variability, and increased time in target) was observed for adolescent and adult participants in the MiniMed 670G system pivotal, regardless of prior CGM experience. These findings indicate that the MiniMed 670G system, an automated HCL insulin delivery and integrated CGM therapy, can similarly manage diabetes outcomes of those who have and have not used CGM in their diabetes care.
Carbohydrate-To-Insulin (CHO:I) Ratio: A Major Factor That Could Influence Daytime Glucose Control Of A Hybrid Closed-Loop System	EASD 2017	The post-hoc analysis of subjects in the HCL pivotal trial demonstrates a lower mean daytime glucose is significantly correlated with the % of insulin delivered as a meal bolus. A more aggressive CHO:I results in a significant improvement in A1C in subjects whose baseline A1C's was 6.5 –7.5%. There was no difference in the demographics of those using the more vs. less aggressive CHO:I
Factors That Influence The Performance Of A Hybrid Closed Loop (HCL) System	ATTD 2017	The analysis of a subgroup of subjects in the HCL pivotal trial indicates a significant effect of aggressive carb-insulin ratio on daytime glucose values. Overall, the system is proven to be safe and demonstrated a positive effect of automating insulin delivery
Personalized Insulin Limits – MiniMed™ Hybrid Closed-Loop Safeguard During Automated Insulin	ATTD 2017	This analysis suggests that insulin limit time- out can likely be extended without increasing the risk of hypoglycemia.
The Variability In Nighttime Insulin Delivery And Glucose Levels With A Hybrid Closed-Loop System In A Pivotal Trial	AACE 2017	From run-in to study phase, reduced A1C & improved in-target, low & high SG values were accompanied by significantly reduced variation in night time SG values. The improvements in night time glycemia appear due to HCL algorithm-controlled insulin delivery ranging from 0 units to a daily-adapted, system-derived individualized maximum insulin limit, automatically adjusted every 5 minutes.

REAL-WORLD DATA & PERFORMANCE OF MINIMED 670G SYSTEM

This data summary leverages the CareLink™ Personal database to compare real-world observations of patients using the MiniMed 670G system with SmartGuard™ hybrid closed loop technology against the pivotal trial and to observe system performance over time. CareLink Personal software is a free web based program that collects information directly from patients' diabetes management system. It generates reports that can be used to monitor and understand more about patients' glucose management while on the MiniMed 670G system. The following summary compares results from real-world data against the pivotal trial and assesses the consistency of system performance.

Data from voluntary uploads of the MiniMed 670G system to the CareLink Personal database have shown both consistent and comparable performance when compared to the MiniMed 670G system pivotal trial data. The timeframe of the data collected is from **Mar 17, 2017 to Aug 28, 2017.** Table 2 defines the characteristics of the data set used, while Table 3 compares real-world data to the results from the pivotal trial and Table 4 shows the consistency of system performance.

Dataset Summary		
Patient accounts	**4,952**	Number of patients with voluntary uploads of the MiniMed 670G system to the CareLink Personal database who fulfill the inclusion criteria
Total Device Days	**176,389**	Sum of calendar days for patients on which there was either insulin infusion or sensor data available on pump.
Total Sensor Days	**153,049**	Sum of calendar days for patients on which there was sensor data available on pump.

Table 2: *Dataset summary from voluntary uploads of MiniMed 670G system to CareLink Personal database from* Mar 17, 2017 to Aug 28, 2017*. For each user, data from the last sensor is excluded from analysis. Data from users with <= 7 days of pump and sensor data is excluded from analysis.*

Table 3 below of real-world data from uploads of the MiniMed 670G system have shown very comparable and consistent trends with the pivotal trial data. In the real world, after Auto Mode had been enabled, patients stayed within a target sensor glucose range approximately 73% of the time, consistent with patients in the pivotal trial. Time spent at or below 70 mg/dL in the real-world data is comparable with the patients in the pivotal trial.[4,9]

	Metrics - Pivotal Trial Data[1] n = 124		**Metrics - Real World Data[2]** n = 4952	
	Initial manual mode	**After Auto Mode enabled**	**Initial manual mode**	**After Auto Mode enabled**
Auto Mode Use (%, Avg)	N/A	88%	N/A	84.4% (18.0%)
Time < +50 mg/dL, Mean (SD)	1.0% (1.1%)	0.6% (0.6%)	0.5% (1.5%)	0.4% (1.0%)
Time <+ 70 mg/dL, Mean (SD)	5.9% (4.1%)	3.3% (2.0%)	3.0% (4.1%)	2.3% (2.9%)
Time In Range (%, 71-180 mg/dL), Mean (SD)	66.7% (12.2%)	72.2% (8.8%)	64.9% (17.1%)	73.0% (11.6%)
Time >+ 180 mg/dL, Mean (SD)	27.4% (13.7%)	24.5% (9.2%)	32.1% (17.9%)	24.7% (11.7%)
Time >+ 300 mg/dL, Mean (SD)	2.3% (4.2%)	1.7% (1.9%)	2.7% (5.5%)	1.5% (2.8%)

Table 3*: Dataset summary comparing voluntary uploads of MiniMed 670G system to CareLink Personal database from* Mar 17, 2017 to Aug 28, 2017*to the MiniMed 670G system Pivotal Trial. For each user, data from the last sensor is excluded from analysis. Data from users with <= 7 days of pump and sensor data is excluded from analysis. Note: all ranges are based on sensor glucose data.*

In the real-world data, the MiniMed 670G system's Auto Mode feature (automated basal delivery) was enabled more than 75% of the time. In addition, once Auto Mode was started, patients continued to stay within a target sensor glucose range approximately 73% of the time (Table 4).

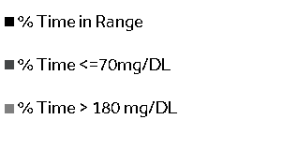
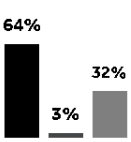
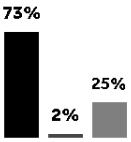
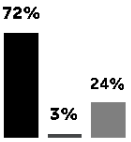
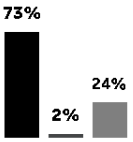
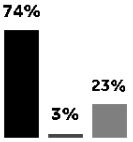
Metrics - Real World Data[1]	Initial Manual Mode	1st 30 calendar days since Auto Mode start	2nd 30 calendar days since Auto Mode start	3rd 30 calendar days since Auto Mode start	4th 30 calendar days since Auto Mode start
Patients available	4,940	4,477	1,095	410	250
Total Sensor days	45,498	77,837	19,422	9,585	5,349
% Time in Auto Mode / patient, Average (Median)	N/A	85.0% (91.3%)	79.1% (88.2%)	77.3% (87.5%)	76.2% (86.7%)
					
Mean SG, Average (SD)	160.1 (52.5) mg/dL	152.1 (48.5) mg/dL	150.9 (48.7) mg/dL	151.3 (48.5) mg/dL	149.2 (48.0) mg/dL
% Time in Range (71-180 mg/dL), Average per patient	64.4%	72.6%	72.5%	72.7%	73.9%
% Time <= 70 mg/dL, Average per patient	3.0%	2.3%	2.7%	2.5%	2.7%
% Time > 180 mg/dL, Average per patient	32.1%	24.6%	24.3%	24.4%	23.0%

Table 4*: Dataset summary spanning 120 days from voluntary uploads of MiniMed 670G system to CareLink Personal database from Mar 17, 2017 to Aug 28, 2017. For each user, data from last sensor is excluded from analysis. Data from users with <= 7 days of pump and sensor data is excluded from analysis.*
Note: all ranges are based on sensor glucose data.

Glossary of Terms

TERM	DEFINITION
Closed Loop	In this context, a system of medical equipment that uses an insulin pump to deliver insulin, a control algorithm to adjust insulin dose delivered and real-time data from a continuous glucose sensor to dynamically and automatically control and manage insulin-dependent diabetes.
Continuous Glucose Monitoring (CGM)	A system of continuous measurement and monitoring of glucose levels throughout the day through use of a sensor placed in the interstitial space
Continuous Subcutaneous Insulin Infusion (CSII)	Therapy for diabetes mellitus where insulin is continuously and automatically infused into the subcutaneous space through an insulin pump
Diabetes Mellitus	A condition of high blood-glucose resulting from the body failing to produce any or a sufficient amount of insulin
Glycemic Control	The medical term used to refer to typical levels of blood glucose or glucose in people with diabetes mellitus
A1C (HbA1C)	Refers to Hemoglobin A1C (HbA1C). A measure of average blood glucose levels over time, expressed as a percent; the target A1C level for non-pregnant adults with diabetes is usually < 7.0%
Hybrid Closed Loop	In this context, a system of medical equipment that uses an insulin pump to deliver insulin, a control algorithm to adjust insulin dose delivered most of the time except when the patient is still required to conduct finger stick tests for correction boluses and calibrations; and real- time data from a continuous glucose sensor to dynamically and automatically control and manage insulin-dependent diabetes.
Hyperglycemia	An excess amount of glucose in the blood and the main result of diabetes mellitus
Hypoglycemia	A deficiency of glucose in the blood; the most common side-effect of insulin treatment for diabetes
Insulin	A hormone produced by the pancreas that facilitates the uptake of glucose in the bloodstream
Insulin Pump	Small, programmable device that uses a tube connected to a catheter to directly administer insulin into the user's subcutaneous tissue
Interstitial Space	The space that surrounds cells of a given tissue; the area in which sensors measure glucose levels
Multiple Daily Injections (MDI)	Therapy for diabetes mellitus where insulin is administered using a needle and syringe, or insulin pen at a frequency ordered by a healthcare professional
Sensor-Augmented Pump (SAP)	Insulin pumps equipped with a sensor to provide continuous glucose monitoring in addition to insulin administration
Self-Monitoring of Blood Glucose (SMBG)	The process of self-monitoring one's blood glucose by acquiring a blood glucose sample, usually by pricking a finger, and reading it through a handheld device
Type 1 Diabetes	Diabetes mellitus that results when the β-cells of the pancreas, which are responsible for the production of insulin, are damaged or destroyed, leading to the cessation of insulin production throughout the body; also referred to as juvenile diabetes or insulin-dependent diabetes mellitus
Type 2 Diabetes	Diabetes mellitus that is characterized by insulin resistance and relative insulin deficiency; also referred to as adult-onset diabetes or noninsulin-dependent diabetes mellitus

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Important Safety Information: MiniMed™ 670G System

The Medtronic MiniMed 670G system is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of type 1 diabetes mellitus in persons, fourteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 670G system includes SmartGuard technology, which can be programmed to automatically adjust delivery of basal insulin based on Continuous Glucose Monitor sensor glucose values, and can suspend delivery of insulin when the sensor glucose value falls below or is predicted to fall below predefined threshold values. The system requires a prescription. The Guardian Sensor (3) glucose values are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. A confirmatory finger stick test via the CONTOUR®NEXT LINK 2.4 blood glucose meter is required prior to making adjustments to diabetes therapy. All therapy adjustments should be based on measurements obtained using the CONTOUR®NEXT LINK 2.4 blood glucose meter and not on values provided by the Guardian Sensor (3). Always check the pump display to ensure the glucose result shown agrees with the glucose results shown on the CONTOUR®NEXT LINK 2.4 blood glucose meter. Do not calibrate your CGM device or calculate a bolus using a blood glucose meter result taken from an Alternative Site (palm) or from a control solution test. It is also not recommended to calibrate your CGM device when sensor or blood glucose values are changing rapidly, e.g., following a meal or physical exercise. If a control solution test is out of range, please note that the result may be transmitted to your pump when in the "Always" send mode.

WARNING: Medtronic performed an evaluation of the MiniMed 670G system and determined that it may not be safe for use in children under the age of 7 because of the way that the system is designed and the daily insulin requirements. Therefore this device should not be used in anyone under the age of 7 years old. This device should also not be used in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

Pump therapy is not recommended for people whose vision or hearing does not allow recognition of pump signals and alarms. Pump therapy is not recommended for people who are unwilling or unable to maintain contact with their healthcare professional. The safety of the 670G system has not been studied in pregnant women. For complete details of the system, including product and important safety information such as indications, contraindications, warnings and precautions associated with system and its components, please consult http://www.medtronicdiabetes.com/important-safety-information#minimed-670g and the appropriate user guide at http://www.medtronicdiabetes.com/download-library

Important Safety Information: MINIMED™ 530g AND minimed™ 630G SYSTEMS WITH SmartGuard™ Technology
The MiniMed 530G and MiniMed 630G systems with SmartGuard technology are intended for the delivery of insulin and continuous glucose monitoring for the management of diabetes mellitus in persons 16 years of age or older who require insulin. Insulin infusion pumps and associated components of insulin infusion systems are limited to sale by or on the order of a physician and should only be used under the direction of a healthcare professional familiar with the risks of insulin pump therapy. Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day. Pump therapy is not recommended for people who are unwilling or unable to maintain contact with their healthcare professional. Pump therapy is not recommended for people whose vision or hearing does not allow recognition of pump signals and alarms. Insulin pumps use rapid-acting insulin. If your insulin delivery is interrupted for any reason, you must be prepared to replace the missed insulin immediately. Replace the infusion set every 48–72 hours, or more frequently per your healthcare professional's instructions. Insertion of a glucose sensor may cause bleeding or irritation at the insertion site. Consult a physician immediately if you experience significant pain or if you suspect that the site is infected. The information provided by CGM systems is intended to supplement, not replace, blood glucose information obtained using a blood glucose meter. A confirmatory fingerstick using a CONTOUR®NEXT LINK portfolio meter* is required prior to making adjustments to diabetes therapy. Always check the pump display when using a CONTOUR®NEXT LINK portfolio meter*, to ensure the glucose result shown agrees with the glucose results shown on the meter. Do not calibrate your CGM device or calculate a bolus using a blood glucose meter result taken from an Alternative Site (palm) or from a control solution test. It is not recommended to calibrate your CGM device when sensor or blood glucose values are changing rapidly, e.g., following a meal or physical exercise. If a control solution test is out of range, please note that the result may be transmitted to your pump when in the "Always" send mode**.** The MiniMed 530G and 630G systems are not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the Suspend on low alarm and take measures to prevent or treat hypoglycemia themselves. Therapy to prevent or treat hypoglycemia should be administered according to the recommendations of the user's healthcare provider.

WARNING: The SmartGuard feature will cause the pump to temporarily suspend insulin delivery for two hours when the sensor glucose reaches a set threshold. Under some conditions of use the pump can suspend again, resulting in very limited insulin delivery. Prolonged suspension can increase the risk of serious hyperglycemia, ketosis, and ketoacidosis. Before using the SmartGuard feature, it is important to read the SmartGuard feature information in the User Guide and discuss proper use of the feature with your healthcare provider.

See www.medtronicdiabetes.com/importantsafetyinformation and the appropriate user guides for additional important details.

*The CONTOUR®NEXT LINK Meter is used with the MiniMed 530G system. The CONTOUR®NEXT LINK 2.4 Meter is used with the MiniMed 630G system.

Important Safety Information: CareLink software
The CareLink software is intended for use as a tool to help manage diabetes. The purpose of the software is to take information transmitted from insulin pumps, glucose meters and continuous glucose monitoring systems, and turn it into CareLink reports. The reports provide information that can be used to identify trends and track daily activities—such as carbohydrates consumed, meal times, insulin delivery, and glucose readings. NOTE: CareLink report data is intended for use as an adjunct in the management of diabetes and NOT intended to be relied upon by itself. Patients should consult their healthcare providers familiar with the management of diabetes prior to making changes in treatment. For more details, please consult http://www.medtronicdiabetes.com/ImportantSafetyInformation and the appropriate CareLink User Guide at http://www.medtronicdiabetes.com/support/download-library/user-guides.

UW Medicine
UNIVERSITY OF WASHINGTON
MEDICAL CENTER

December 7, 2017

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To whom it may concern:

I am a faculty member at the University of Washington and have been the medical director of the Diabetes Care Center since we opened in 1991. I have watched diabetes treatments, both medications and technologies evolve over the decades for both type 1 and type 2 diabetes. For type 1 diabetes, I have seen proliferative retinopathy in this country improve from 50% to under 10% and for diabetic kidney disease, we've seen rates reduced from over 30% to under 5%. And with type 2 diabetes, we've learned how our new diabetes drugs can reduce cardiovascular mortality by over 25-35% over 3 to 5 years. It is always interesting for me to review this recent history with our medical students.

Unfortunately, our treatments are far from perfect. While we are doing better than we did 30 years ago, we are not doing as well with the tools we have, and access to both beneficial drugs and technologies continue to be a major public health challenge.

I was involved in many of the initial continuous glucose monitoring (CGM) studies over a decade ago, and remained involved today with CGM in general in addition to artificial pancreas work. At both the national and international level, I've been involved in educating physicians how to best use CGM for their patients. Like all new technologies, there were early adopters and the technology was crude by today's standards. But like self-monitoring of blood glucose, this has become the standard of care for many patients. It is important to note that "good diabetes control" should not be limited to HbA1c. A "good" HbA1c below 7% is not "good" if associated with hypoglycemia requiring the assistance of a family member. One problem with many studies is that the only hypoglycemia documented are those episodes requiring paramedic or emergency room visits. We now appreciate that hypoglycemia, often without symptoms after many years of diabetes, can have devastating effects on brain function and cognition.

I appreciate that the clinical trials with CGM have been reviewed by your committee. One criticism of diabetes technology trials is actual real-world experience does not reflect clinical trial data. The T1D Exchange is a data registry of American patients with type 1 diabetes of all ages. Currently over 16,000 patients in 76 centers are followed, most of these academic clinics.

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Compared to 2010-2012, CGM use has increased:

Age (years)	Enrolled 2010-2012 (%)	May 2016-July 2017 (%)
< 6	4	49
6-<13	4	32
13-<18	3	20
18-<26	4	21
26-<50	15	37
50-<65	16	35
>65	10	24

Overall, use has increased from 7% to 28%. Over a third of adults younger than 65 years-old used CGM, as our oldest population did not have Medicare coverage (this started in the summer of 2017). Note that a quarter of these type 1 patients of Medicare age used this technology, without reimbursement from Medicare. Most of these patients have no awareness to their hypoglycemia.

HbA1c (May 2016-July 2017) was lower for each age group using CGM (adjusting for age, duration, race/ethnicity, pump status, income, SMBG, clinic site, $p < 0.001$):

Age (years)	Non-CGM Users (HbA1c%)	CGM Users (HbA1c%)
< 13	8.7	7.9
13-<26	9.2	8.4
>26	7.9	7.4

HbA1c levels were also lower in CGM users across ethnicities regardless of insulin delivery method (N = 16,656).

In the T1D Exchange, like my clinic at the University of Washington, 60% of patients use insulin pumps. It should be emphasized, however, that the more common insulin delivery outside of our academic centers is with multiple injections, and the T1D Exchange showed improvements with both forms of insulin delivery. Up until now, (at least for the past few years), the only option for multiple injection patients was the Dexcom CGM. In an earlier analysis, the T1D Exchange showed 75% of pump patients used this device. The Dexcom has something that in my mind is under-emphasized to those who are not familiar: the “Share App”. This allows family members or friends to be able to watch the CGM data, “real-time” on their smart phones, and be alerted when the blood glucose levels rise too high or drops too low. I have parents use this with their teenage children, and it’s even more frequently used for family members of my elderly patients with type 1 diabetes. This is a population that gets minimum visibility in the press, but is growing quickly due to improvements in care for type 1 diabetes. We know from earlier studies in this population average time hypoglycemic ranges from 83 to 99 minutes per day (mean age 67 years, mean duration of diabetes 40 years). These patients have minimum awareness to sense their hypoglycemia, which is one reason why Medicare approved CGM in 2017. In fact, our T1D Exchange group also showed that seizure or coma from hypoglycemia occurs in about 20% of patients *per year* after 40 years of diabetes, independent of age when CGM is not used.

While we don’t have specific randomized controlled trial data for the benefit of reducing hypoglycemic exposure in this older population (or specific trials with the Share App), we are now performing a study called WISDM (Wireless Innovation for Seniors with Diabetes Mellitus) funded by the Helmsley Charitable Trust and the Juvenile Diabetes Research Foundation. Nevertheless, since we now appreciate

hypoglycemia unawareness is so profound and dangerous leading to cardiac arrhythmias and death, Medicare agreed it needed to be covered for these patients.

While an early study clearly showed that CGM reduced overall diabetes-related complications (Diabetes Care 2010;33:1269-1274), uptake a decade ago was minimal due to the challenges with the early devices, particularly with accuracy. Modern-day CGMs are now quite accurate to the point the FDA has allowed non-adjunctive use (no fingerstick glucose levels to dose insulin) with the Dexcom and Abbott Libre, and a hybrid closed loop with Medtronic. It also needs to be realized that most of the devastating microvascular complications from childhood-onset type 1 diabetes occurs after 10 to 20 years duration of diabetes. In other words, hypoglycemia becomes both the most important clinical aspect of care in addition to the rate-limiting part of insulin treatment. The trajectory of CGM in my adult clinic in Seattle has CGM penetration well over 50% in type 1 diabetes, and in Medicare-age patients I anticipate over 80% within the next year simply to protect from the risks of disabling hypoglycemia.

One final point: CGM has allowed us to see how poor HbA1c is as a biomarker. We now know that in patients without renal disease, liver disease, or anemia, a HbA1c of 8% could mean the average glucose on CGM could range between 130 and 210 mg/dL. In fact, one person with a HbA1c of 9% could actually have a lower mean glucose than someone else with a HbA1c of 7%! We now understand we all glycate hemoglobin at different rates and hemoglobin has different lifespans in different people. We now teach our students, residents, and fellows to treat the glucose, not the HbA1c as for individual patients, it is often extremely misleading. While treating glucose based on 3 to 4 finger-sticks is certainly better than what we had in the 1960s and 1970s, that doesn't nearly give the granularity required to best dose insulin and minimize hypoglycemia.

Thank you in advance for your consideration of covering CGM for all patients who could benefit from this technology. It has revolutionized our ability to care for our patients with diabetes. Please feel free to contact me with any questions.

Sincerely,

Irl B. Hirsch, MD
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December 7, 2017
RE: DRAFT Report: Continuous Glucose Monitoring--Update

On behalf of Seattle Children's and the Pediatric Endocrine Division of the Department of Pediatrics, University of Washington, we are responding to the draft report of "Continuous Glucose Monitoring—Update":

Below are our key points and references listed below:

1. As clinicians, we have certainly observed that use of CGM has been a huge benefit for children and caregivers. It has led to changes in self-management around timing of insulin, food, and exercise. Such changes in self-management (or caregiver management in the case of younger children) are not often captured in clinical trials. CGM real-time data can now be shared between children, parents and caregivers outside the home (e.g., at school) in real-time. This has led to significant improvements in coordination of care, reduced parental fear of hypoglycemia, and greater collaboration between patients, parents, and schools.

2. There are very few RCT's in youth with CGM and the biggest ones were conducted using older versions of CGM that were significantly less accurate, more painful, and had shorter duration of use. In part because of these factors, patients were less likely to use CGM. Participant use was low, particularly in adolescents, and that low use lead to limited effectiveness. However, even then, consistent CGM use was associated with improvements in glycemic control. Acceptance is much better now, with modern CGM being far more comfortable and accurate, and having a longer sensor life.

3. The report does not specifically address automated insulin delivery such as recent FDA approval and hybrid closed loop therapy (already in wide use clinically). CGM is also intrinsic to hypoglycemia prevention modes such as "low threshold suspend" and "predictive low glucose suspension", both of which are now FDA approved and in wide use by youth. CGM is an essential part of automated insulin delivery. HCL has been clearly demonstrated to decrease rates of nocturnal hypoglycemia and increased time in desired glucose range. Use of CGM and pumps with low threshold suspend has also been associated with reduced hypoglycemia.

4. This report minimizes findings (often by pooling two or more studies) and often reports low evidence.

5. Glycemic variability is not emphasized. Reduction of glycemic excursion and time in (desired) range are now key measures in studies assessing diabetes outcomes.

6. Quality of life and fear of hypoglycemia are not emphasized. These are extremely important, as they impact self-management behaviors. Key bodies, such as the JDRF, now strongly advocate that we measure care outcomes and overall diabetes control more broadly than just HbA1c, with specific outcomes of value including: variability, quality of life, rates of hypoglycemia, and fear of hypoglycemia.

7. There are additional references that should be considered, including recent international consensus guidelines and a recent abstract presented at ISPAD 2017.

8. Data from recent studies shows the benefits of CGM in exercise in youth. With CGM, youth can more safely participate in vigorous physical activity without severe or recurrent hypoglycemia. CGM has been

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shown to provide real world guidance on safe management. This guidance is superior to single point in time finger-stick blood glucose measurements in active youth. Critically, closed loop automated insulin delivery has now been shown to maintain glucose time in range and reduce hypoglycemia in exercise settings where frequent blood glucose monitoring is not safe or practical, such as in cold alpine climates, during skiing. These and other studies show clearly that CGM use is associated with safer physical activity in youth with type 1 diabetes, a key driver of better cardiovascular outcomes and quality of life.

9. Data from two observational studies, Type 1 Diabetes Exchange and the DPV, jointly show improvements in A1c with CGM. This is much more striking in 2016 compared to 2011 (see ISPAD abstract). Type 1 Diabetes Exchange, clearly demonstrates improved glycemic control in those using CGM across race/ethnicities. Unfortunately, disparities exist in use of diabetes technologies, including CGM (from Type 1 Exchange and the SEARCH for Diabetes in Youth study). Racial/ethnic minorities and children from lower income families are disproportionately represented by public health insurance plans. We should be working to address these health care disparities, rather than exacerbating them (see abstract below).

Title: Continuous Glucose Monitoring (CGM) and Glycemic Control among Youth with Type 1 Diabetes (T1D): International comparison from the T1D Exchange (T1DX) and the DPV Initiative

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Objectives: To assess change in rates of pediatric CGM use over the past 5 years, and how it impacts glycemic control. Data from 2 registries were compared: the US-based T1DX and the German/Austrian DPV.
Methods: Registry participants aged <18yrs with T1D duration ≥ 1yr encompassed 29,003 individuals in 2011 and 29,124 participants in 2016. Demographic data, CGM use and A1c were obtained from medical records.
Results: CGM use increased in all age groups in both registries, and was most pronounced in the youngest patients (Table). In 2011, CGM use did not alter A1c in DPV participants (7.8% vs 7.9%, p=0.26); yet, in 2016, A1c was lower in CGM users (7.5% v 7.9%, P<0.001). For T1DX CGM users, lower A1c was seen in both 2011 (7.9% v 8.6%, P<0.001) and 2016 (8.1% v 9.0%, P<0.001). In 2016, mean A1c was lower among CGM users regardless of insulin delivery method compared to pump only (P<0.001) and injection only (P<0.001) in both T1DX and DPV registries. In 2016, CGM users were more likely to achieve glycemic targets (A1c <7.5%) for DPV (58.1% v 42.9%, P<0.001) and T1DX (32.3% v 14.6%, P<0.001).
Conclusions: Pediatric CGM use increased in both registries and was associated with improved glycemic control regardless of insulin delivery modality. As penetrance of this technology is lowest in adolescents, a group noted to have the highest mean A1c, strategies to engage this cohort of youth in adoption and long-term use of CGM are needed.

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Additional references:

Measures of glycemic variability in T1D and the effect of real-time continuous glucose monitoring (El-Laboudi et al DTT, Dec 2017). Targeting postprandial glycemia in children with diabetes: opportunities and challenges (Geyer MC et al Diab Obesity Metab 2017)

Practical consideration on the use of CGM in pediatrics and older adults and nonadjunctive use ((Forlenza GP et al DTT 2017)

International consensus on use of CGM (Danne T et al, Diabetes care 2017)

Assessing the effectiveness of a 3-month day-and-night home closed-loop control combined with pump suspend feature compared with sensor-augmented pump therapy in youths and adults with suboptimally controlled type 1 diabetes: a randomized parallel study protocol. (Bally L et al, BMJ Open 2017)

Self-monitoring using CGM with real-time feedback improves exercise adherence in individuals with impaired blood glucose: a pilot study. Bailey KJ et al, Diabetes Technology & Therapeutics, 2016

Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: an observational field study Riddell et al, Diabetes Technol Ther. 2011

Closed-Loop Control during Intense Prolonged Outdoor Exercise in Adolescents with Type 1 Diabetes: The Artificial Pancreas Ski Study. Breton MD, Diabetes Care. 2017

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To whom it may concern:

I am writing regarding Continuous Glucose Monitor (CGM) coverage for patients with diabetes, before pregnancy and during pregnancy.

In 2008, Metzger et al. published the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) Study. This pivotal study has defined glycemic management in pregnancy since its publication. The study concluded that even mild hyperglycemia is toxic to the fetus. Under-treated or poorly controlled diabetes in pregnancy is associated with several adverse pregnancy outcomes including recurrent early pregnancy loss, fetal anomalies (in particular CNS, skeletal and cardiac anomalies), preterm birth, fetal death, preeclampsia, polyhydramnios, IUGR, and macrosomia. Abnormal HbA1c exponentially increases the risk for fetal anomalies. The HAPO study found that an A1c over 10 increased fetal anomaly risk to over 50%. There is an increased incidence of cesarean section and birth trauma. Newborns from diabetic mothers have an increased incidence of delayed lung maturity, neonatal respiratory distress syndrome, jaundice, polycythemia, hypoglycemia, hypothermia, and hypocalcemia. These outcomes can lead to costly NICU admits and prolonged maternal hospital stay.

A continuous glucose monitor is the most effective tool for lowering average blood glucose and HbA1c, decreasing time spent hypo- AND hyperglycemic and improving patients safety every day. Multiple studies including the COMISAIR study, the STAR1 and STAR3 studies, a study by Foster et al., the SWITCH study and now the DIaMonD study all show statistically significant improvements in aforementioned outcomes. Including ~30% decrease time in the hypo- and hyperglycemic ranges. Decreased episodes in severe range hypoglycemia (<50 mg/dL). Decreased HbA1c by ~1 after 24 weeks.

For women who are planning pregnancy, a CGM allows them to have tight control prior to conception. It is not enough to have good control during pregnancy because costly structural fetal anomalies are caused by hyperglycemia during organogenesis before most women even know they are pregnant. If a patient isn't on birth control and is sexually active, they could be pregnant and not know it. For those fetuses, it is too late if they developed sacral agenesis or a cardiac defect because of maternal hyperglycemia. A decrease in A1c of 1 could mean the difference between a healthy baby and a fetal anomaly.

Patients with Type 1 Diabetes at the Center for Maternal Fetal Medicine consistently have better maternal and fetal outcomes when they have a CGM. It is imperative these patients keep their BG range under 120 with fasting blood glucose less than 90mg/dL. This level of control inevitably puts the patient at a greater risk for hypoglycemia. CGMs make this control possible and keeps the patient safe and alive. Poor maternal and fetal outcomes associated with uncontrolled diabetes are preventable.

Prior to new diabetes technology, infertility plagued women with type 1 diabetes. The incidence of miscarriage was higher as was the incidence of fetal anomalies. However, with pumps and CGMs, patients are able to get pregnant and have a healthy baby.

The loss of CGM coverage, for pregnant patients or patients who want to be pregnant, would be devastating.

Please feel free to contact us with any additional questions.

Respectfully,

Alyson K Blum, PharmD, CDE
The Center for Maternal Fetal Medicine Diabetes Care Team

NATIONAL DIABETES
VOLUNTEER LEADERSHIP COUNCIL

December 8, 2017

Health Technology Clinical Committee (HTCC)
Cherry Street Plaza
626 8th Avenue SE
Olympia, WA 98501

Re: Washington State Re-Review of CGM

Dear Committee Members,

I am writing you today on behalf of the National Diabetes Volunteer Leadership Council (NDVLC) to ask for your support for consideration of a rationale coverage determination for Washington State Medicaid recipients for continuous glucose monitoring. This coverage policy would provide access to life saving technology for these patients. Continuous Glucose Monitoring (CGM) for patients with diabetes who use insulin to manage their condition is helping patients better manage their diabetes, which, in turn, reduces the cost burden to the state. Better managed diabetes results in better clinical and economic outcomes.

At the American Diabetes Association's Annual Scientific Sessions held this past June (June 8-12, 2017) in San Diego, there were many discussions, symposia and clinical trial results that validated the beneficial impact of CGM on patients with diabetes. CGM is now the Standard of Care for patients using insulin and who are struggling to reach their clinical goals as established by their care teams.

The NDVLC would like your consideration for a policy that makes access to the technology reasonable and a process that is not onerous for their care providers. The citizens of Washington State are counting on you for your support so they may have access to a standard of care that is truly lifesaving technology.

The Medicare Coverage determination has a good balance for your consideration.

> According to the framework currently established by CMS, a therapeutic CGM may be covered for any individuals with **Type 1 or Type 2 diabetes on intensive insulin therapy** when all of the following criteria are met:
>
> > The beneficiary has diabetes mellitus; ***and***
> > The beneficiary has been using a home blood glucose monitor (BGM) and performing frequent (four or more times a day) BGM testing; ***and***

The beneficiary is insulin-treated with multiple daily injections (MDI) of insulin or a continuous subcutaneous insulin infusion (CSII) pump; ***and***
The beneficiary's insulin treatment regimen requires frequent adjustment by the beneficiary based on therapeutic CGM testing results.

Documentation would be a completed CMN with PA.
Please keep in mind that patients on insulin, are at a higher risk for untoward events

The membership of the NDVLC is composed of individuals who have previously served in top leadership positions at national voluntary diabetes related health organizations. We are involved in diabetes advocacy on the local, state and national levels on behalf of the 29 million Americans who are living with diabetes.

We are asking for your consideration of a coverage policy which balances patient access with making the administrative burden manageable for the healthcare team.

Sincerely,

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President, National Diabetes Volunteer Leadership Council
(and 2005-2006 Chair of the Board, American Diabetes Association)
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http://ndvlc.org/how-we-work/

cc: National Diabetes Volunteer Leadership Council Board of Directors

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Dear Members of the HTCC,

Thank you for accepting public comments on CGM, a revolutionary technology that has seen significant scientific advances in recent years. Although the FreeStyle Libre system was included in the assessment (Table 1, Page 20), evidence on its accuracy, clinical outcomes, and economic outcomes was not mentioned in the detailed report. On behalf of Abbott Diabetes Care, Inc., we are writing to provide scientific support of the clinical and economic effectiveness of a unique, factory-calibrated CGM device, the FreeStyle Libre system, especially given the clear evidence for hypoglycemia reduction and improved adherence to glucose monitoring in adult populations with either T1 or T2 diabetes.

The FreeStyle Libre system is the first and only FDA approved CGM device for adults with diabetes that does not require blood sample calibration and is indicated to replace blood glucose testing over 10 days of wear. It has been submitted to the Centers for Medicare and Medicaid Services for durable medical equipment coverage under the Part B Medical Benefit, satisfying all requirements as therapeutic CGM.[11]

Additional comments related to the inclusion of time in range as one of the primary intermediate outcomes, discontinuation of the FreeStyle Navigator system in the U.S., and the NICE Medtech

Innovation Briefing Report on the FreeStyle Libre system are included in Section III for consideration.

I. Clinical Evidence and Guidelines of CGM

An expert panel of physicians, researchers and individuals experienced in CGM technologies was convened at the ATTD meeting in February 2017 and tasked with developing a consensus statement on CGM use. The International Consensus on the Use of CGM was created and published in the December 2017 issue of Diabetes Care. This is the latest in a series of expert guidelines regarding the use and effectiveness of CGM[13]. The consensus classified CGM into two main categories: real-time use (rtCGM) and intermittently viewed (iCGM). Given that patients proactively use the FreeStyle Libre reader to read its sensor, the consensus committee referred to the FreeStyle Libre system as iCGM. Following review of the latest clinical evidence, the committee recommended that "CGM should be considered in conjunction with HbA1c for glycemic status assessment and therapy adjustment in all patients with type 1 diabetes and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia"[13]. The committee also recommended, "CGM data should be used to assess hypoglycemia and glucose variability" (p. 1633).

II. Clinical and Economic Evidence of the FreeStyle Libre System in Adults with Diabetes

Below is a review of the major clinical studies showing the accuracy, effectiveness and safety of the FreeStyle Libre system (FSL) in people with diabetes (PWD).

1. Accuracy

The performance of the FSL system was evaluated in a clinical study conducted at four centers with 48 participants with diabetes (95.8% Type 1, 4.2% Type 2).[26] All participants were aged 18 and older. Participants in the study required insulin to manage their diabetes. Each participant wore up to two FSL sensors on the back of the upper arm. During the study, participants tested their blood glucose using fingerstick capillary samples at least eight times during each day of the study. Participants used the blood glucose meter built into the FSL reader. Additionally, venous blood glucose was analyzed up to 128 times over four separate visits to the clinical center. Venous blood was analyzed using the Yellow Springs Instrument Life Sciences 2300 STAT Plus™ Glucose & Lactate Analyzer (YSI). YSI is a laboratory glucose and lactate analyzer of whole blood and plasma and is a widely recognized standard in laboratory analysis of blood glucose. Glucose readings obtained from the system were compared to glucose readings obtained from the YSI to evaluate the performance of the system. Three lots of sensors were evaluated in the study. Agreement between FreeStyle Libre glucose measurement and YSI reading of venous blood glucose was used to evaluate the accuracy of CGM versus YSI reference. Overall, 91.1% of results were within ±20 mg/dL / 20% of YSI reference. The overall accuracy was also measured by comparing the Mean and Median Absolute Relative Difference between the FSL and reference YSI glucose values. The Mean or Median Absolute Relative Difference gives an indication of the average percent disagreement between the CGM and the reference. Based on the 5,772-paired readings, the Mean Absolute Relative Difference was 9.7% for the comparison with YSI reference. The Median Absolute Relative Difference shows that half of the time the system was within 7.7% of the YSI reference.

Agreement between the FSL and capillary blood glucose values (BG) as measured by the reader's built-in meter was characterized by using paired FreeStyle Libre glucose measurement and BG value. Overall, 84.3% of results were within ±20 mg/dL / 20% of BG values. Based on 3,680-paired readings, the Mean Absolute Relative Difference was 12.1% for the comparison with BG value. The Median Absolute Relative Difference showed half of the time the system was within 9.4% of the BG value.

No device related serious adverse events occurred during the study. Mild skin irritations, such as erythema, edema, rash, bleeding, itching, induration, and infection were reported around the insertion site and adhesive area by a moderate frequency of participants (5 out of 48 or 10.4%). Pain was mostly reported as none, with only one instance of mild pain.

For more information regarding the accuracy of the FreeStyle Libre system, please refer to the user's manual available at https://freestyleserver.com/Payloads/IFU/2017_sep/ART38553-001_rev-C-Web.pdf

2. Efficacy and Safety

a. In Adults with T1DM

The IMPACT trial was a randomized study comparing the FSL system with the current standard of care (self-monitoring of blood glucose, SMBG) in people with T1DM[9]. Patients were enrolled from 23 European diabetes centers. The primary outcome of the study was change in time in hypoglycemia (<70 mg/dL) between baseline and 6 months. After the screening and baseline phase, 120 participants were randomly assigned to the intervention group and 121 to the control group, with outcomes being evaluated in 119 and 120, respectively. Mean time in hypoglycemia changed from 3.38 h/day at baseline to 2.03 h/day at 6 months (baseline adjusted

mean change −1.39) in the intervention group, and from 3.44 h/day to 3.27 h/day in the control group (−0.14); with the between-group difference of −1.24 (SE 0.239; $p<0.0001$), equating to a 38% reduction in time in hypoglycemia in the intervention group. The reduction in hypoglycemia exposure (time and events) was similar during both daytime and nighttime, and the pattern of daily scanning showed that the highest frequency occurred in the evening, indicating patients most likely took the necessary adjustments to their insulin or carbohydrate intake before sleep. There were also significant between-group differences favoring the intervention group compared with the control group in the glycemic variability measures. The mean number of self-monitored blood glucose tests performed per day by the intervention group immediately reduced from 5.5 (SD 2.0) tests per day in the 14-day baseline phase to 0.5 (0.7) test per day during the treatment phase of the trial. This was an unprompted response by intervention participants that clinically equates to approximately one self-monitoring blood glucose test every 2 days. The mean number of sensor scans per day for the intervention group was 15.1 (SD 6.9) during the treatment phase. Importantly, assessing patient reported outcomes showed that patient satisfaction with treatment was significantly improved for intervention compared with control (adjusted between-group difference −0.24 [SE 0.049]; $p<0.0001$). The total treatment satisfaction and perceived frequency of hyperglycemia were also significantly improved in the intervention group compared with the control group. No device-related hypoglycemia or safety issues were reported. There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device. It can be concluded from the IMPACT study that the FSL system safely reduced the time adults with well-controlled type 1 diabetes spent in

hypoglycemia, decreased glycemic variability, increased time in range and improved key patient reported outcomes.

b. In Adults with T2DM

FSL has been also studied in people with T2D[17]. In an open-label, randomized controlled study (REPLACE), adults with type 2 diabetes, on intensive insulin therapy from 26 European diabetes centers, were enrolled. Following 2 weeks of blinded sensor wear, 2:1 (intervention/control) randomization was to intervention (FSL) or control (SMBG). Primary outcome was difference in HbA1c at 6 months in the full analysis set. Prespecified secondary outcomes included time in hypoglycemia, effect of age, and patient satisfaction. Participants (n = 224) were randomized into the two groups (149 intervention, 75 controls). At 6 months, while there was no difference in the change in HbA1c between intervention and controls (-0.29 ± 0.07% [mean ± SE] and -0.31 ± 0.09%, respectively; p = 0.8222), a difference was detected in favor of FSL in participants aged <65 years (-0.53 ± 0.09% and -0.20 ± 0.12%, respectively; p = 0.0301). Time in hypoglycemia <70 mg/dL reduced by 0.47 ± 0.13 h/day (mean ± SE; p = 0.0006), and <55 mg/dL reduced by 0.22 ± 0.07 h/day (p = 0.0014) for intervention participants compared with controls, equating to reductions of 43% and 53%, respectively. SMBG frequency, similar at baseline, decreased in intervention participants from 3.8 ± 1.4 tests/day (mean ± SD) to 0.3 ± 0.7, and remained unchanged in controls (average of 3.9 ± 1.5 test/day at baseline and 3.8 ± 1.9 at the end of the study). The mean number of sensor scans per day for the intervention group was 8.3 (SD 4.4) during the treatment phase. Treatment satisfaction was higher in intervention compared with controls (DTSQ 13.1 ± 0.50 [mean ± SE] and 9.0 ± 0.72, respectively; p < 0.0001). No serious adverse events or severe hypoglycemic events were reported related to sensor data use.

In summary, the REPLACE study demonstrated that the use of FSL in type 2 diabetes treated with intensive insulin therapy resulted in no difference in HbA1c change but did reduce hypoglycemia, thus offering a safe and effective replacement for SMBG.

In a 12-month follow-up of 139 patients, enrolled in the REPLACE trial and having completed the 6-month treatment phase who continued into the open-access phase for an additional 6 months, time in hypoglycemia (sensor glucose 70 mg/dL) was reduced by 50% compared to baseline (-0.70 ± 1.85/24 h [mean ± standard deviation]; p = 0.0002) at 12 months[18]. Nocturnal hypoglycemia (2300 to 0600 hours, <70 mg/dL) was reduced by 52%; p = 0.0002. There was no change in time in range (sensor glucose 70-180 mg/dL). SMBG testing fell from a mean of 3.9 (median 3.9) times/day at baseline to 0.2 (0.0), with an average frequency of sensor scanning of 7.1 (5.7) times/day at 12 months. During this 6-month extension period, no device-related serious adverse events were reported. Nine participants reported 16 instances of device-related adverse events (e.g. infection, allergy). This follow up cohort demonstrates that the use of FSL for glycemic management in individuals with type 2 diabetes treated with intensive insulin therapy over 12 months was associated with a sustained reduction in hypoglycemia and safely and effectively replaced SMBG.

3. Real-world Evidence

De-identified data from all FSL users willing to participate were included in a real-world database. When connected to the computer-based software with an active internet connection, the FSL reader's 90-day memory was de-identified and uploaded to the database. The aim was to evaluate association of real-world scanning with the FreeStyle Libre system and glucose control measures. For analysis, sensors were required to have at least 120 hours of use. From

September 2014 to May 2016, data were collected from 50,831 readers with 279,446 sensors, comprising a total of 86.4 million monitoring hours (63.8 million scans). Twenty equally-sized groups were created based on lowest to highest rate of scanning (n = 2542 each). Six regions were identified, the five countries having the highest device use (Germany, Spain, France, UK and Italy), and a sixth "region" grouped all remaining countries. Scan rate per reader was determined and twenty equally-sized rank-ordered groups, categorized by scan frequency, were evaluated. Glucose scan frequency was analyzed together with relationship to glycemic markers in each of these regions. These analyses were reported at ATTD, ADA and EASD in 2017[1,14,15]. Real-world users of the FreeStyle Libre system scanned at a high frequency. The users performed a mean of 16.3 scans per day (median, 14; interquartile range, 10–20), with a mean of 1.6 scans per day between midnight and 6 AM. These data show that people using the FreeStyle Libre system typically monitor their glucose at a frequency that meets or exceeds that recommended by guidelines[2,24], a much higher rate than that typically achieved using SMBG. The high scanning frequency in the database is similar to the frequency observed in the IMPACT trial, demonstrating the high level of acceptance of the device by patients in a real-world setting. SMBG testing was low, with a median of 0.36 tests per day via the built-in meter, confirming the IMPACT trial finding that people did not feel the need to routinely supplement their glucose monitoring via the FreeStyle Libre system with additional SMBG.

Additionally, the higher rates of scanning were significantly associated with improved glucose control. As scan rate increased from the lowest group (mean 4.4 scans per day) to the highest (mean 48.1 scans per day), the time spent in the target glycemic range (70–180 mg/dL) increased from 12.0 to 16.8 hours per day (40% increase; $p < 0.001$), and time spent in hyperglycemia ($\geq$

180 mg/dL) decreased by 44%, from a mean (SD) of 10.5 ± 5 to 5.9 ± 5 hours per day ($p < 0.001$). The duration of time spent in hypoglycemia reduced significantly, with greater reductions seen in more severe hypoglycemic states: time below 70, 55, and 45 mg/dL decreased by 15%, 40%, and 49% respectively (all $p < 0.001$). All metrics were improved for individuals scanning at the median frequency (14 scans per day), compared with the lowest-scanning group. Estimated HbA1c in the highest scanning frequency group was significantly lower than in the group that scanned least frequently (6.7% vs 8.0%; $p < 0.001$), and there was a consistent trend towards lower estimated HbA1c as scanning frequency increased.

Average scan frequency varied significantly across regions: the highest mean scan frequency was in the UK, where participants scanned a mean of 18.0 (median, 15; IQR, 11–23) times per day and the lowest scan frequency in France, at 13.6 (median, 12; IQR, 8–17) scans per day. Participants in France spent the longest time in hypoglycemia, with a mean (± SD) of 58 (± 65) to 40 (± 62) minutes per day with glucose < 55 mg/dL in the lowest and highest frequency scanning groups, respectively. Individuals from Italy spent the least amount of time in hypoglycemia, with a mean (± SD) of 33 (± 59) to 20 (± 35) minutes per day with glucose < 55 mg/dL in the lowest and highest frequency scanning groups, respectively.

The real-world database represents an extremely large population utilizing the FreeStyle Libre system, which allows detailed assessment of measures of hyperglycemia, hypoglycemia, and self-monitoring behaviors. Limitations of the database include a lack of specific demographic data, precluding precise conclusions regarding users with type 1 or type 2 diabetes. The database also does not include data on glucose control before participants started using the FreeStyle Libre system, and conclusions about the impact of initiating system use cannot be made.

4. Cost-effectiveness Analysis

The FSL system was launched in Europe in 2014 and Canada in the summer of 2017. Following FDA approval in September 2017, the FSL system was launched in the US in November.

The assessment of cost-effectiveness of the FSL system has been based on the IQVIA Core Diabetes Model (CDM)[23]. (IQVIA were formerly known as IMS). The CDM has been used for both T1 and T2 MDI populations by pharmaceutical and medical device manufacturers, including other CGM manufacturers. CDM has been used to demonstrate the cost-effectiveness of the FSL system compared with SMBG in various European countries and Australia, based on inputs from the IMPACT and REPLACE RCTs. The T1 and T2 versions of CDM for the FSL also include a health utility increment (0.03) for the FSL compared with SMBG that was obtained from a time trade-off study [22]. This study quantified the preference of a general population for using a factory calibrated CGM, such as the FSL system to monitor glucose levels as an alternative to SMBG.

Enclosed are posters presented at ISPOR (Boston, USA 2017) demonstrating the cost-effectiveness of the FSL in T1 and T2 MDI, based on the CDM from the perspective of the UK National Health Service (NHS) [6,27]. The base case for T1 MDI shows an ICER of $33,810/QALY (GBP 25,045 assuming an exchange rate of $1.35 to a British pound) and the base case for T2 MDI shows an ICER of $32,187/QALY (GBP 23,842). These base case results were supported by various scenarios, hence it was concluded that the FSL system is cost-effective for both T1 and T2 MDI populations based on a typical UK willingness-to-pay threshold of about GBP 30,000/QALY.

The findings from the UK base case and scenarios are supported by the CDM produced for Sweden that was presented at ISPOR (Vienna, Austria 2016). These posters also included base case results from Germany, Italy, France, Netherlands, and Australia [5, 21]. These results support the conclusion that the FSL system is cost-effective across a range of health systems for both T1 and T2 MDI populations.

Additional exploratory evidence for the cost-effectiveness of the FSL system in T1 and T2 MDI from a Swedish perspective was recently presented at ISPOR (Glasgow, 2017), although this time incorporating the real-world evidence from over 50,000 readers[14]. These models show that the reductions in HbA1c and hypoglycemia that are associated with the increased frequency of glucose monitoring observed in the real world for FSL compared with SMBG support the cost-effectiveness of the FSL [7,8].

The posters for these various CDM presentations are enclosed. Manuscripts are being submitted to journals in early 2018 for publication.

There are various limitations of the cost-effectiveness models for the FSL, although these are similar to the limitations noted for the models for other CGM devices in the draft evidence report. The REPLACE and IMPACT studies were 6 months in duration, the models are not based on American healthcare inputs, and the manufacturer sponsors them. However, the ICERs provided for the FSL system for the T1 MDI population are below the lower end of the range provided by the previous studies of CGM devices. For the T2 MDI population, the ICER for the FSL system is of similar magnitude to that obtained for the T1 MDI population. Note that although this ICER for a T2 MDI population is greater than that from the only other T2 cost

effectiveness study of a CGM device in the draft evidence report, the model for the FSL was based on continuous use of the device whereas the other study was based on intermittent use. The limitations of the FSL cost-effectiveness models should also be considered alongside several reasons why the ICERs for the FSL system could be considered conservative, especially when compared with previous studies of CGM devices included in the draft evidence report:

- **Diminishing Disutility for Hypoglycemia Events compared with Fixed Disutility per Event:** Previous assessments of CGM devices[10] typically assumed a fixed disutility per non-severe hypoglycemic event (NSHE). Recent literature has shown disutility per NSHE declines with increased rates of NSHE[20], and so the average disutility per event is lower than that assumed for the earlier method [4,12]. All other things being equal, the more recent diminishing marginal disutility method as used for the FSL CDM, will tend to produce much higher ICER values than the fixed disutility method used in previous assessments. For reference, scenario 11 in Table 3 and Figure 1 of the UK NHS poster for T1 MDI shows this assumption makes a large difference to the ICER.
- **No Difference in Severe Hypoglycemia Events assumed in Base Case for FSL CDM:** The base case for the FSL CDM assumed no difference in severe hypoglycemia events (SHE) compared with SMBG, but the IMPACT and REPLACE studies showed a substantial reduction in hypoglycemic events less than 40mg/dl in favor of the FSL (55% in IMPACT, 48% in REPLACE). There is likely to be a large reduction in SHEs for the FSL that is similar to that assumed for other CGMs[10]. For example, assuming a 55% reduction in SHEs, based on events less than 40mg/dl from the IMPACT study as a proxy, the ICER for FSL in

We would also like to mention that since 2011, FreeStyle Navigator is no longer commercially available in the United States. Based on the major differences in product feature and performance between the FreeStyle Navigator and the FreeStyle Libre systems, we will leave the discretion to the reviewers whether or not the FreeStyle Navigator system should still be included in this report.

In addition to the NICE guidelines on integrated sensor-augmented pump therapy and diabetes diagnosis and management for type 1 diabetes on pages 26-28, we would like to supply the NICE Medtech Innovation Briefing on the FreeStyle Libre for Glucose Monitoring, published on July 3 2017[25]. The report recognizes the FreeStyle Libre system "as an alternative to routine blood glucose monitoring in people with type 1 and 2 diabetes who use insulin injections."

In conclusion, the use of CGM is a game-changer in the management of PWD. This revolutionary technology provides an affordable and cost-effective solution to enable PWD to gain breadth of knowledge of their glycemic measures beyond hyperglycemia, namely hypoglycemia and glycemic variability. The use of the FSL has been proven to reduce time in hypoglycemia in patients with both T1D and T2D, significantly reduce the need for SMBG and improve certain patient reported outcomes, importantly diabetes treatment satisfaction.

Sincerely,

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Cost-effectiveness of a flash glucose monitoring system based on real-world usage for type 1 diabetes (T1DM) patients using intensive insulin: a Swedish perspective

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Background & Objective

- In patients with Type 1 diabetes (T1DM), the pancreas has stopped producing insulin, the hormone that stores sugars and other carbohydrates in cells. These patients must frequently measure their blood-glucose level and administer insulin to alleviate symptoms of the disease.
- Routing glucose monitoring is especially valuable for T1DM patients using intensive insulin, and more frequent testing is associated with lower HbA1c (Miller 2013).
- A factory-calibrated flash glucose monitoring ("FM") system (the FreeStyle Libre™ system) continuously measures glucose levels from interstitial fluid using minimally-invasive wired enzyme technology and thus without requiring routine self-monitoring of blood glucose (SMBG). Data is then transferred to a handheld reader from the wearable arm sensor, which lasts up to 14 days.
- Real-world data has been collected from over 50,000 FM readers (Dunn 2017).
  - These readers indicate that patients scan 16 times/day on average compared to 5-6 tests/day for SMBG users (Miller 2013). *Note: Baseline data and cohort information are not available for this real-world dataset.*
  - These cross-sectional data also show an association between lower HbA1c and more frequent scans (see **Figure 1**).
- Therefore, this study evaluates the cost-effectiveness of increased glucose test frequency based on this real-world data, comparing FM vs SMBG in T1DM patients using intensive insulin.

Methods

- CDM Overview
  - The QuintilesIMS CDM (v9.0), a non-product specific model that can be used to assess the long-term health and economic consequences of diabetes interventions, was used in this analysis.
  - The model has been published previously in detail; it has likewise been validated extensively against clinical and epidemiological studies (Palmer 2004; McEwan 2014), and accepted as a valid model for use in HTA decisions (e.g. UK NICE DG 21, TA151, TA203, TA248, TA288, and TA336).
  - The QuintilesIMS CDM uses Monte Carlo simulation in 17 parallel Markov model structures to estimate outcomes such as major complications of diabetes, costs, life expectancy, and quality-adjusted life years (QALYs).
  - The model utilised data from the DCCT study (DCCT 1995) to estimate HbA1c progression, while other physiological parameters progressed according to data from the Framingham Heart Study (Wilson 1993).
- Analytic Overview
  - This analysis employed bootstrapping with 1,000 simulation iterations containing 1,000 patients each over a 50-year time horizon; this approach was taken to create robust estimates and minimize Monte Carlo error.
  - The simulation estimates direct costs, life years (LYs), and QALYs over the time horizon, using a 3% discount rate on costs and effects (Läkemedelsförmånsnämndens allmänna råd om ekonomiska utvärderingar 2003), with costs reported in 2016 SEK.
- Model Inputs and Assumptions
  - Cohort Characteristics **(Table 1)**
    - The cohort reflects the IMPACT clinical trial population, including those aged 18 years or over with well-controlled T1DM and HbA1c of ≤7.5% (58 mmol/mol) and treated by multiple daily injections of insulin or continuous subcutaneous insulin infusion for a minimum of 6 months (Bolinder 2016). Patients were testing glucose levels at least 10 times per week and were technically capable of using FM.
    - Any inputs unavailable from the IMPACT study were derived from the published literature.

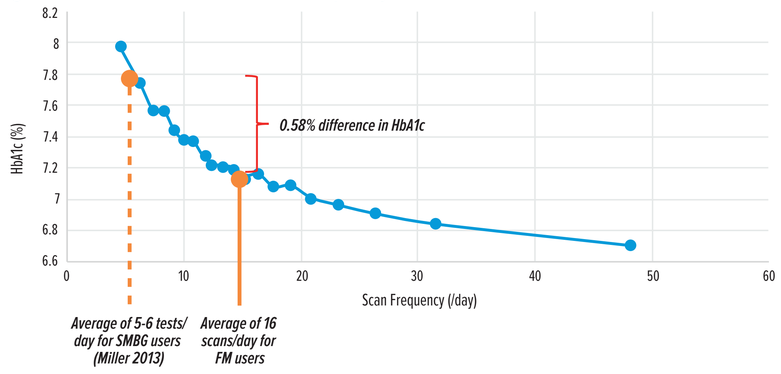
Table 1: Patient Cohort Characteristics

	Value (mean)	Units
Demographics[1]		
Start age	43.7	years
Duration of Diabetes	22	years
Male	56.9%	
Baseline risk factors		
HbA1c[1]	6.78%	
Systolic blood pressure (SBP)[1]	126.00	mmHg
Diastolic blood pressure (DBP)[1]	75.00	mmHg
Total cholesterol (T-CHOL)[1]	193.00	mg/dL
HDL[1]	72.00	mg/dL
LDL[1]	106.00	mg/dL
Triglycerides (TRIG)[1]	76.00	mg/dL
Body mass index (BMI)[1]	25.00	kg/m^2
Estimated glomerular filtration rate (eGFR)[2]	91.70	mL/min/1.73m^2
Haemoglobin[3]	14.50	g/dL
White blood cells (WBC)[3]	6.80	10^6/mL
Heart rate[4]	68.00	bpm
Waist to hip ratio (WHR)[5]	0.93	
Urinary albumin excretion rate (uAER)[6]	3.10	mg/mmol
Serum creatinine[5]	1.10	mg/dL
Serum albumin[5]	3.90	g/dL
Proportion smoker[1]	14.3%	
Cigarettes/day[1]	1.00	
Alcohol consumption[1]	1.58	oz/week

Sources: 1. IMPACT trial (Bolinder 2016); 2. Nathan 2014; 3. Hayes 2013; 4. Paterson 2007; 5. Folsom 2003; 6. Davis 2010

  - Treatment Effects **(Table 2)**
    - Based on the real-world sensor data, the average number of scans per day (16) is associated with an HbA1c value that is 0.58% lower than that for the average number of SMBG per day in this population (5-6/day; Miller 2013). See **Figure 1**.

Figure 1. Association between scan frequency and HbA1c



    - Non-severe hypoglycaemia rates reflect the IMPACT trial symptomatic event rate for SMBG.
      - Sensor-based data from the trial showing that FM reduced daytime non-severe hypoglycaemia events (NSHEs) by 25.5% and nocturnal NSHEs by 33.2% compared to SMBG was used to adjust this parameter for the FM arm.
      - No treatment effect was assumed in the base case for severe hypoglycaemic events (SHEs), as the trial was not designed to detect a difference in this rate. An equal rate for the two strategies was derived from published literature (UK Hypoglycaemia Study Group 2007).
      - For the model, a proxy of 70 mg/dL is used for non-severe hypoglycaemia, and 55 mg/dL for more severe hypoglycaemia, based on American Diabetes Association guidelines (ADA 2017).
    - A recent TTO study (Matza 2017) found a mean utility improvement of 0.03 (95% CI 0.023-0.038) associated with FM compared with routine SMBG.
  - Other Utility Values
    - The baseline utility for T1DM was obtained from the literature (Clarke 2002) (Table 2), while the remaining utility and disutility values were derived from T2DM publications given the lack of available inputs specific to T1DM.
    - For NSHEs, the model leveraged the Lauridsen 2014 publication to employ a diminishing disutilities approach through the built-in functionality in the model. The literature has shown that for the first few events, patients experience a higher disutility. The disutility per event decreases as patients become accustomed to experiencing NSHEs.

Table 2. Key Model Inputs

Key inputs	FM	SMBG	Source
Physiological parameters			
Change from baseline HbA1c (IQR), %-points	0.58 (0.36, 0.73)	0 (0.0)	Dunn 2017
Adverse events			
Default SHE2 rate, per 100 pt-years	37.76	37.76	UK Hypo Study, Foos 2015
Default SHE1 rate, per 100 pt-years	282.24	282.24	UK Hypo Study, Foos 2015
NSHE rate, per 100 patient-years	4,897.10	6,760.00	IMPACT trial (Bolinder 2016)
Proportion of events that are nocturnal	25%	27%	IMPACT trial (Bolinder 2016)
Utilities			
Annual utility score associated with treatment	0.03	0.00	Matza 2015
Baseline T1DM	0.785		Clarke 2002
Disutility for SHE2 (during daytime)	-0.055		Evans 2013
Disutility for SHE2 (nocturnal)	-0.057		Evans 2013
Disutility for SHE1 (during daytime)	-0.0183		Marrett 2011
Disutility for SHE1 (nocturnal)	-0.0183		Marrett 2011
Disutility for NSHE	Diminishing approach		Lauridsen 2014
T1DM Intervention Costs			
Annual cost, year 1	SEK 22,143	SEK 9,891	Calculation
Annual cost, year 2+	SEK 20,716	SEK 9,891	Calculation
Key Acute Event Costs			
SHE2 (requiring medical assistance)	SEK 5,036		Jonsson 2006; Anderson 2002; DCCT 1991
SHE1 (requiring nonmedical third party help)	SEK 0.00		Assumption
NSHE	SEK 0.00		Assumption

** Only upper IQR showed a difference in hypo events; lower IQR is aligned with the mean*

  - Costs & Resource Utilisation
    - All costs (2016 SEK) are derived from public sources (medications, consumables) or the published literature (e.g. costs of complications). Intervention-specific costs reflect least expensive forms of consumables (pharmaceuticals and glucose monitor test strips) available from TLV, and the cost list from Skåne, Södra regionvårdnämnden 2015 informed physician fees.
    - Annual costs **(Table 2)** associated with managing T1DM were calculated according to unit prices and trial-based resource utilisation, including:
      - FM Costs
        - » 26 sensors per year (1 every 2 weeks); 1 reader every 2 years;
        - » IMPACT trial resource use: 182.5 back-up blood glucose test strips per year, 267.4 lancets per year, 45.8 units of insulin per day, and one additional physician visit in the first year to ensure appropriate use of the device.
      - SMBG Costs
        - » IMPACT trial resource use: 1,971 strips per year, 657.6 lancets per year and 38.4 units of insulin per day.
  - Analyses
    - Total costs, effects, and an incremental cost-effectiveness ratio (ICER) were calculated for the base case analysis.
    - Scenario analyses (see **Table 3**) were performed to explore the effect on HbA1c of the scan frequency interquartile range (IQR, approximately 10 and 20 scans/day, respectively), and the impact of scan frequency on hypoglycaemic event rates at base case and IQR scan levels (measured vs serious (<55 mg/dL) hypoglycaemic event rate associated with scanning at same frequency as SMBG users in literature).

Table 3: Scenario Analyses

Scenario	Description	Change in HbA1c (%)		Difference in rate of hypoglycemic events <55mg/dL (%)	
		FM	SMBG	FM	SMBG
Base case	HbA1c effect only (16 scans/day FM vs 5-6 scans/day SMBG)	-0.58%	0%	0%	0%
SA1	Adding SHE to base case HbA1c impact	-0.58%	0%	-7.15%	0%
SA2	Upper IQR, HbA1c effect only	-0.73%	0%	0%	0%
SA3	Upper IQR, HbA1c and SHE effects	-0.73%	0%	-11.00%	0%
SA4	Lower IQR, HbA1c effect only*	-0.36%	0%	0%	0%

**Note that lower IQR scan frequency showed no impact on major hypoglycaemic event rates, and thus led to no additional scenario analysis*

Results

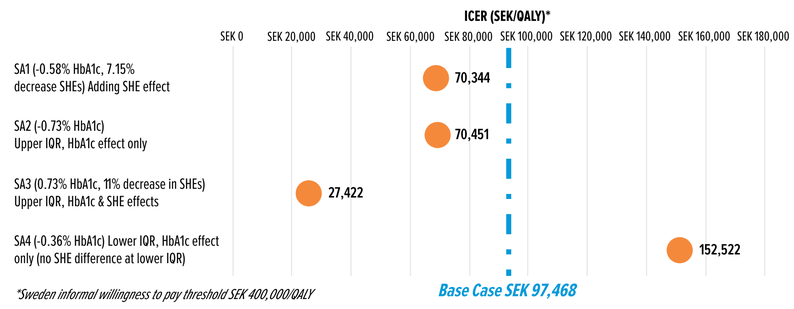
- Base Case Analysis (**Table 4**)
  - The base case ICER (cost/QALY) is SEK 97,468
    - With real-world FM sensor data indicating differential glucose testing frequency, this translated over the 50-year time horizon to 1.071 more QALYs attributable to lower HbA1c, fewer NSHEs, and the utility benefit associated with FM.
    - The incremental cost of FM versus SMBG (SEK 141,982 direct costs, and SEK 104,397 in combined direct and indirect costs) reflect the increased cost of the intervention, as well as reduced costs associated with managing downstream diabetes-related complications.
    - This implies that using FM may be considered a cost-effective strategy compared to an unofficial SEK 400,000/QALY threshold given the assumptions employed in this analysis.

Table 4. Base Case Cost-Effectiveness Results

	FM	SMBG	Increment
LY	21.39	21.16	0.23
QALY	13.60	12.53	1.07
Direct Costs	SEK 1,112,006	SEK 970,024	SEK 141,982
Combined Costs	SEK 1,786,017	SEK 1,681,620	SEK 104,397
ICER (Direct SEK/QALY)			SEK 132,557
ICER (Combined SEK/QALY)			SEK 97,468

  - Scenario analyses remained favorable as well, ranging from SEK27,422 to SEK152,522/QALY, and thus well under the hypothetical willingness-to-pay threshold.

Figure 2. Scenario Analyses



Limitations

- The main intervention effects in this study are based on cross-sectional real-world data.
  - Lack of glucose metrics prior to use of FM mean that there is no ability to assess the causal link between initiating use of FM and HbA1c decline.
  - However, the data do show a clearly higher average test frequency for FM patients (scanning 16x/day vs average 5-6x/day SMBG) and the associated average HbA1c is indeed lower for this population.
  - It remains valuable to understand that if FM leads to higher test frequency, the HbA1c effects and thus cost-effectiveness results will reflect those found in this analysis.
  - However, scenarios remain speculative due to the lack of longitudinal data on the impact of increasingly frequent scanning on HbA1c and rates of serious hypoglycaemic events (<55mg/dL).
- It is not possible to determine patient characteristics associated with each reader in the real-world dataset.
  - The effects may be from a mixed Type 1 and Type 2 diabetes population.
  - There may be additional behavioural differences associated with frequent FM use, and these may independently affect outcomes, e.g. regarding adherence to dietary or medication plans.
  - This analysis therefore should therefore be considered exploratory, given use of mixed population sensor data together with trial-based T1DM population characteristics.

Conclusion

- This exploratory analysis suggests that there may be HbA1c and hypoglycaemia effects that translate to long-term health and economic benefits due to higher glucose test frequency for patients using FM compared to SMBG.
- Given these benefits, FM may be cost-effective for T1DM patients receiving intensive insulin in Sweden.
- Based on the potential economic benefit seen in this exploratory analysis, future research should evaluate the real world FM test frequency in a T1DM population receiving intensive insulin, as well as demonstrate the longitudinal impact of changing test frequency.

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PMD74

Cost effectiveness analysis of a flash glucose monitoring system for Type 1 diabetes (T1DM) patients receiving intensive insulin treatment in Europe and Australia

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Background

- Type 1 diabetes (T1DM) is a chronic condition in which a person's pancreas stops producing insulin, a hormone that promotes uptake of glucose from the bloodstream into cells where it is stored as an energy source for the body. Patients with T1DM must frequently measure their blood glucose level and administer insulin in order to alleviate symptoms of the disease and reduce the risk of long-term complications
- A novel, minimally-invasive flash glucose monitor (the FreeStyle Libre™ system, "FM") has been developed to continuously measure glucose levels from interstitial fluid using wired enzyme technology
  - The glucose level data are updated every minute and data are collected for 15-minute intervals and wirelessly transferred to a handheld reader with each scan of the sensor, which may be worn on the back of the upper arm for up to 14 days
  - The reader stores up to 90 days of data transferred 8 hours at a time, and provides glucose trends without requiring routine lancing and blood samples for self-monitoring of blood glucose (SMBG)
- In intensive insulin-treated T1DM patients, the IMPACT trial, as recently published in The Lancet, showed that using FM reduced time spent in hypoglycaemia compared to using standard SMBG, while substantially decreasing the number of blood glucose tests (Bolinder 2016)
- In addition, a recent time trade-off study (TTO) indicated utility improvement associated with FM (Matza 2015)
- However, the relative economic value of using FM vs. SMBG has not yet been evaluated with evidence from the recent trial

Objective

- To estimate the cost-effectiveness of using FM vs. SMBG through the IMS Core Diabetes Model (IMS CDM) for intensive insulin-treated T1DM patients for Europe and Australia, using Sweden as the core case, with additional results for Germany, Italy, France, Netherlands, and Australia

Methods

- CDM Overview
  - The IMS CDM (v9.0), a non-product specific, multiplayer internet application to assess the long-term health outcomes and economic consequences for diabetes treatments, was used in this analysis. The IMS CDM has been published previously in detail, and its results have been validated against clinical and epidemiological studies (Palmer 2004, McEwan 2014). It has also been accepted as a valid model for use in health technology assessment (HTA) decisions (e.g. UK NICE DG 21, TA151, TA203, TA248, TA288, and TA336)
  - The IMS CDM combines Markov model structures and Monte Carlo simulation to capture major complications of diabetes and additional results including costs, life expectancy, and quality-adjusted life years (QALYs)
  - The model utilized data from the DCCT study (DCCT 1995) in T1DM for HbA1c progression, while other physiological parameters progressed according to data from the Framingham Heart Study (Wilson 1993)
- Analytic Overview
  - This analysis used version 9.0 of the CDM. A bootstrapping simulation approach was implemented for a 50 year time horizon with 1,000 simulation iterations containing 1,000 patients each; this approach was taken to create robust estimates and minimize Monte Carlo error
  - The simulation estimates direct costs, LYs, and QALYs over the time horizon, employing country-specific discount rates, with results reported in 2015 currency
  - For the core case, the analysis was conducted for T1DM patients in Sweden, where the study perspective is societal according to Sweden economic evaluation guidelines (Läkemedelsförmånsnämnden. Läkemedelsförmånsnämndens allmänna råd om ekonomiska utvärderingar 2003). Unit cost data as well as indirect data are from Sweden-specific publications and data sources
  - For other countries, perspectives reflect country-specific published guidance (payer or societal), and all country costs were obtained from public databases or published sources
- Model Inputs and Assumptions
  - Cohort Characteristics (**Table 1**)
    - The clinical trial population are those aged 18 years or over with well-controlled T1DM and HbA1c of ≤7.5% (58 mmol/mol) and treated by multiple daily injections of insulin or continuous subcutaneous insulin infusion for a minimum of 6 months (Bolinder 2016). Patients were testing glucose levels at least 10 times per week and were technically capable of using FM
    - The patient characteristics in the analyses reflect the IMPACT trial population
    - For CDM inputs unavailable from the IMPACT study, estimates from the published literature were used

Table 1: Patients Characteristics

	Value (mean)	Units
Demographics[1]		
Start age	43.7	years
Duration of Diabetes	22	years
Male	56.9%	
Baseline risk factors		
HbA1c[1]	6.78%	

Sources: 1. Bolinder 2016

- Model Inputs and Assumptions
  - Treatment Effects (**Table 2**)
    - The IMPACT trial of patients with good glycaemic control (N=241) showed an HbA1c increase of 0.12% from baseline in both treatment arms. Specifically, HbA1c increased by 0.12% from the baseline value in both arms of the IMPACT trial. It was assumed that HbA1c progressed over the time based on the DCCT study, increasing 0.045 each year in T1DM (DCCT Group 1995)
    - The baseline rate of symptomatic hypoglycaemic events across the two arms was applied to the SMBG arm. The sensor-based data from the trial showed that after 6 months, FM reduced daytime non-severe hypoglycaemia events (NSHEs) by 25.5% and nocturnal NSHEs by 33.2% compared to SMBG
    - The overall number of SHEs are assumed equal for both arms, with a rate derived from published literature (UK Hypoglycaemia Study Group 2007)
  - Utility Values (**Table 2**)
    - The TTO study found a mean utility improvement of 0.03 associated with FM (CI 95%: 0.023-0.038)
    - For NSHEs, the model leveraged the Lauridsen 2014 publication to employ a diminishing disutilities approach through the built-in functionality in the model. The literature has shown that patients experience higher disutility for the first events, with disutility per event decreasing over time

Table 2: Key Inputs in the Base Case

Key inputs	FM	SMBG	Source
Physiological parameters			
Change from baseline HbA1c (%-points)	0.12 (0.45)	0.12 (0.45)	Bolinder 2016
Adverse events			
SHE2 events (/100 patient-years)	37.76	37.76	UK Hypo Study, Foos 2015
SHE1 events (/100 patient-years)	282.24	282.24	UK Hypo Study, Foos 2015
NSHEs rate (/100 patient-years)	4,897.10	6,760.00	Bolinder 2016
Proportion of events that are nocturnal	25%	27%	Bolinder 2016
Utilities			
Annual utility score associated with treatment	0.03	0.00	Matza 2015
Baseline T1DM	0.785		Clarke 2002
Disutility for SHE2 (during daytime)	-0.055		Evans 2013
Disutility for SHE2 (nocturnal)	-0.057		Evans 2013
Disutility for SHE1 (during daytime)	-0.0183		Marrett 2011
Disutility for SHE1 (nocturnal)	-0.0183		Marrett 2011
Disutility for NSHE	Diminishing approach		Lauridsen 2014
Indirect Costs			
Retirement age	65		OECD 2013
Age at first income	18		Assumption
Mean salary male (annual)	SEK 385,028.36		Statistics Sweden 2014
Mean salary female (annual)	SEK 331,052.43		Statistics Sweden 2014
No. work days/year	210		Ekonomifakta 2014

Note: SHE2: Severe hypoglycaemic event requiring professional medical care; SHE1: severe hypoglycaemic event requiring third party assistance; NSHE: non-severe hypoglycaemic event

- Model Inputs and Assumptions
  - Costs & Resource Utilization (**Table 3**)
    - All costs (2015 currency) are derived from national databases (medications, procedures) or the published literature (costs of complications), except for the FM intervention costs which are based on manufacturer data
    - Annual costs associated with managing T1DM were calculated based on country-specific unit prices and trial-based resource utilization, including:
      - FM Costs
        - 26 sensors per year (1 every 2 weeks) for all countries except France (27 sensors). Local market assumptions of reader reimbursement were used
        - IMPACT trial resource use was applied: 182.5 back-up blood glucose test strips per year, 267.4 lancets per year, 45.8 units of insulin per day (except in Australia, where 38.5 units of insulin were assumed for both arms) and one additional physician visit in the first year (except for Germany where no additional physician visits were considered) to ensure appropriate use of the device
      - SMBG Costs
        - IMPACT trial resource use was applied: 1,971 strips per year, 657.6 lancets per year and 38.4 units of insulin per day
- Scenario analyses were also performed to test the robustness of base case results (**Table 4**)

Table 3: Key Modeling and Cost Inputs

	SWE[1]	GER[1]	ITA[1]	FRA[1]	NL[1]	AUS[1]
Modeling Considerations						
Perspective[2]	Societal	Statutory health insurance	Italian national health service	Collective national health insurance	Societal	Health care system
Willingness to pay ICER/QALY threshold[3]	SEK330,000	€50,000*	€31,000-96,000	€30,000-90,000	€20,000-80,000	$30,000-70,000
Discount Rate[2]						
Costs	3.00%	3.00%	3.00%	4.00%	4.00%	5.00%
Clinical outcomes	3.00%	3.00%	3.00%	4.00%	1.50%	5.00%
T1DM Intervention Costs						
Annual FM cost (year 1)	SEK20,261	€2,287	€2,292	€3,597	€2,246	A$2,916
Annual FM cost (year 2+)	SEK18,835	€2,287	€2,272	€3,561	€2,227	A$2,879
Annual SMBG cost (year 1+)	SEK9,892	€1,461	€1,674	€2,746	€1,439	A$1,393
Key Acute Events Costs[4]						
SHE2	SEK5,036	€2,528	€1,391	€4,154	€3,343	A$2,635
SHE1	SEK0	€0	€0	€0	€0	A$42
NSHE	SEK0	€0	€0	€0	€0	A$0

Note: 1. SWE-Sweden, GER-Germany, ITA-Italy, FRA-France, NL-Netherlands, AUS-Australia; 2. Source by country: SWE- Läkemedelsförmånsnämnden. Läkemedelsförmånsnämndens allmänna råd om ekonomiska utvärderingar 2003; GER - IQWIG 2015; ITA-Capri 2001; FRA-Haute Autorité de Santé 2012; NL-Dutch Guidelines for Pharmacoeconomic Research 2006; 3. Source by country: SWE – Cleemput 2008, GER – Krejczy 2014, Neumann 2011, Merkesdal 2010; ITA- WHO 2015; FRA- Hamers 2012 and WHO 2015; NL-Simoens 2010; AUS – Australian Government Department of Health; 4. Source by country:SWE- Jonsson et al 2006; Anderson et al 2002; DCCT 1991; GER-InEK 2013a; InEK 2013b; ITA-Allegato 1, Gazette Uffiziale, 2013; FRA- Torreton 2013; NL-Hammer 2009; AUS- Ly TT 2014

**Hypothetical willingness to pay ICER/QALY threshold*

Table 4: Scenario Analyses

	Scenario	Description
1	Discount rate	Investigate impact of 0% discount rather than base case country-specific defaults
2	Time horizon	Explore shorter time horizons of 5 and 10 years
3	NSHE rate	Reduce the NSHE rate in SMBG arm to 29.00 events/patient year, which is derived from the UK Hypo study (UK Hypo study 2007). The NSHE rate in FM arm was reduced by the same percentage of daytime and nocturnal events as reported in the IMPACT trial
4	FM treatment utility	Vary treatment – related utility benefit in FM arm using the 95% CI (0.023 to 0.038)
5	Physiological parameters	Leverage trial-based physiological parameters' change rather than the assumption of 0 change
6	Resource utilization - year 1	Vary the treatment cost associated with SMBG for year 1 only, given observed extra resource utilization from the clinical trial. Remove the cost of severe events to avoid double counting
7	Resource utilization - all years	Vary treatment cost associated with SMBG for all years, given observed extra resource utilization from the clinical trial. Remove the cost of severe events to avoid double counting
8	SHE assumption	Assume all SHEs require medical third party assistance and use an alternative SHE disutility value from the literature (Currie 2006), reflecting categories available in the prior version of the CDM (version 8.5)
9	SHE reduction	Reduce the rate of SHEs by 55.0% for the FM arm, rather than 0% in the base case, based on a reduction in sensor-based hypoglycemic events <40 mg/dL from the clinical trial

Results

- Base case analyses (**Table 5**)
  - For Sweden, the base case ICER cost/(QALY is SEK240,826, whereas the cost/NSHE-averted is SEK281
    - Over the 50-year time horizon, FM use led to higher QALYs due to fewer NSHEs and the utility benefit associated with the FM arm
    - The incremental cost of FM versus SMBG is attributed exclusively to the intervention cost in the base case
    - The ICER/QALY was well below the willingness to pay threshold of SEK 330,000
  - For other included countries, the base case scenario produces ICERS ranging from €14,209 to €22,099 and A$39,786 (Australia)
    - Results reflect a similar pattern to Sweden, with cost differences exclusively due to the FM system
- All ICER estimations for these countries remain below published country-specific thresholds, suggesting that FM is cost-effective across the range of countries in this analysis

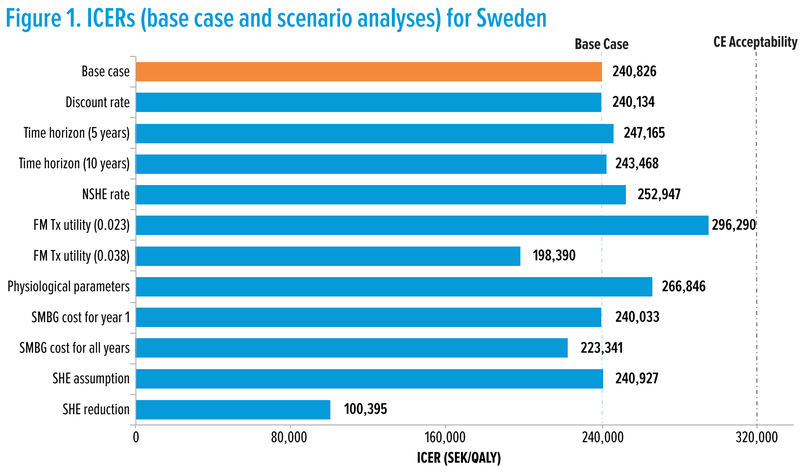
Table 5: Base Case Results

	FM			SMBG			Incremental				
Country	Costs	LYs	QA-LYs	Costs	LYs	QA-LYs	Costs	LYs	QA-LYs	ICER/QALY	Costs/NSHE-averted
Sweden*	SEK 1,182,024	21.10	13.26	SEK 989,051	21.10	12.46	SEK 192,973	0.00	0.80	SEK 240,826	SEK 281
Germany*	€ 156,868	20.72	12.93	€ 139,467	20.72	12.15	€ 17,401	0.00	0.79	€ 22,099	€ 26
Italy	€ 83,924	20.24	12.63	€ 71,595	20.33	11.59	€ 12,329	0.00	0.77	€ 16,008	€ 25
France	€ 141,080	18.35	11.51	€ 125,882	18.35	10.81	€ 15,198	0.00	0.70	€ 21,862	€ 31
Netherlands*	€ 164,108	26.42	16.34	€ 147,999	26.42	15.33	€ 14,331	0.00	1.01	€ 14,209	€ 21
Australia	A$107,100	15.48	9.74	A$83,754	15.48	9.15	A$23,346	0.00	0.59	A$39,786	A$36

*Note: * Direct and indirect costs are included here*
NB: Country-specific survival curves lead to life year differences between countries

- Scenario analyses
  - For Sweden (**Figure 1**), among the scenario analyses performed, a 20% reduction in utility benefit had the largest impact on ICER in terms of SEK/QALY. In this case it rose to SEK296,290, yet remains below the Swedish threshold
  - When performing scenario analyses for the other countries, results reflect the same pattern as in Sweden; the largest impact on the ICER in terms of QALYs stems from a 20% reduction in utility benefit of FM

Figure 1. ICERs (base case and scenario analyses) for Sweden



Interpretation

- CDM
  - Although the CDM is well-validated, the impact of short-term outcomes associated with hypoglycemic events are not fully captured in the model and may be under-estimated (NICE 2016)
    - The CDM assumes that NSHEs are not associated with the occurrence of severe events, although this relationship has been shown in a recent study (Sreenan 2014)
    - The CDM does not incorporate the effects of hypoglycemic unawareness, which can increase the risk of experiencing severe hypoglycemic events. Given how much previously unrecognised hypoglycaemia FM was able to detect in IMPACT, it may be that its use could help people avoid hypoglycaemic unawareness and thereby reduce risk of severe events
- Clinical
  - The main clinical data and patient characteristics for the analysis are taken from a 6-month trial, and may not represent the real-world patient population or effects of FM. However, there were no trial protocol-mandated monitoring or adjustments to therapy, and results may be thought to approximate real-world use
- Inputs
  - Current utility values may underrepresent the quality-of-life impact of using FM
    - The intervention-associated utility benefit, derived from a time tradeoff study, assumed that FM offsets the need for blood tests performed on average 3 times per day by SMBG users. However, guideline recommendations to test 6-10 times per day in T1DM may mean even greater utility benefit
    - The disutility associated with minor (<70mg/dl) hypoglycaemic events is assumed to reflect the diminishing effect of each event as they become more frequent. However, this value is much smaller than that used in prior economic analyses (Currie 2006), and therefore, the ICERs in this study are likely to be conservative relative to other published values
- Given these considerations, there is potential for FM to be even more cost-effective than SMBG versus the analyses conducted

Conclusion

- This analysis of FM vs SMBG shows that improved hypoglycaemia outcomes and health utility benefit translate into economic value with incremental costs per QALY under published thresholds in Sweden, as well as in the other countries included in this analysis
- Results were robust in scenario analyses, and thus FM may be considered cost-effective for use in T1DM patients with good glycaemic control using intensive insulin

Sponsored by Abbott Diabetes Care

Cost-effectiveness of a flash glucose monitoring system based on real-world usage for type 2 diabetes (T2DM) patients using intensive insulin: a Swedish perspective

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Background & Objective

- Type 2 diabetes (T2DM) occurs when the body produces insufficient insulin for its needs. Insulin is a hormone that allows cells to store sugar and other carbohydrates as a potential future energy source for the body. As resistance to insulin grows, the body produces more insulin to compensate, but eventually the body is unable to produce a sufficient amount. Initially, patients are instructed to change their lifestyle habits (e.g. exercise and diet), but patients will likely require pharmacologic treatment, including insulin therapy.
- When patients are on insulin therapy, they are instructed to monitor their blood glucose in order to adequately manage the disease and prevent downstream complications;
  - For T2DM patients using intensive insulin, more frequent testing is associated with lower HbA1c (Schutt 2006).
- A novel, factory-calibrated flash glucose monitoring ("FM") system (the FreeStyle Libre™ system) continuously measures glucose levels from interstitial fluid using wired enzyme technology and thus without requiring routine self-monitoring of blood glucose (SMBG). Data is then transferred to a handheld reader from the wearable arm sensor, which can be used for up to 14 days.
- Real-world data has been collected from over 50,000 FM readers (Dunn 2017).
  - These readers indicate that patients scan 16 times/day on average compared to approximately 2.7 times/day for SMBG users (Schutt 2006). *Note: No baseline data or cohort information are available.*
  - These cross-sectional data also show an association between lower HbA1c and more frequent scans (see **Figure 1**).
- Therefore, this study evaluates the cost-effectiveness of increased glucose test frequency based on this real-world data, comparing FM vs SMBG in T2DM patients using intensive insulin.

Methods

- CDM Overview
  - The QuintilesIMS CDM (v8.5), a non-product specific model that can be used to assess the long-term health and economic consequences of diabetes interventions, was used in this analysis.
  - The model has been published previously in detail; it has likewise been validated extensively against clinical and epidemiological studies (Palmer 2004; McEwan 2014), and accepted as a valid model for use in HTA decisions (e.g. UK NICE DG 21, TA151, TA203, TA248, TA288, and TA336).
  - The QuintilesIMS CDM uses Monte Carlo simulation in 17 parallel Markov model structures to estimate outcomes such as major complications of diabetes, costs, life expectancy, and quality-adjusted life years (QALYs).
  - The model utilized data from the UKPDS study to estimate HbA1c progression, while other physiological parameters progressed according to data from the Framingham Heart Study (Wilson 1993).
- Analytic Overview
  - This analysis employed bootstrapping with 1,000 simulation iterations containing 1,000 patients each over a 40-year time horizon; this approach was taken to create robust estimates and minimize Monte Carlo error.
  - The simulation estimates direct costs, life years (LYs), and QALYs over the time horizon, using a 3% discount rate on costs and effects (Läkemedelsförmånsnämndens allmänna råd om ekonomiska utvärderingar 2003), with costs reported in 2016 SEK.
- Model Inputs and Assumptions
  - Cohort Characteristics **(Table 1)**
    - The cohort reflects the REPLACE clinical trial population, including those aged 18 years or over with poorly controlled T2DM and HbA1c of 7.5% to 12.0%. Patients were also required to be treated with either multiple daily injections of insulin or receive continuous subcutaneous insulin infusion for at least 6 months (Haak 2017). Additionally, SMBG was used at least 10 times per week and patients were required to be technically capable of using FM.
    - Any inputs unavailable from the REPLACE study were derived from the published literature.

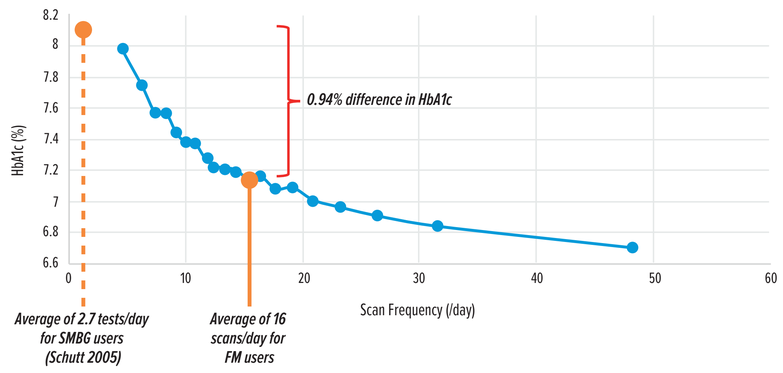
Table 1: Patient Cohort Characteristics

	Value (mean)	Units
Demographics[1]		
Start age	59.2	years
Duration of Diabetes	17.0	years
Male	67.0%	
Baseline risk factors		
HbA1c[1]	8.68%	
Systolic blood pressure (SBP)[1]	137.00	mmHg
Total cholesterol (T-CHOL)[1]	186.00	mg/dL
HDL[1]	49.00	mg/dL
LDL[1]	99.00	mg/dL
Triglycerides (TRIG)[1]	208.00	mg/dL
Body mass index (BMI)[1]	33.2	kg/m^2
Estimated glomerular filtration rate (eGFR)[2]	77.5	mL/min/1.73m^2
Haemoglobin[2]	14.5	g/dL
White blood cells (WBC)[2]	6.80	10^6/mL
Heart rate[2]	72.00	bpm
Proportion smoker[1]	14.3%	
Cigarettes/day[1]	3.00	
Alcohol consumption[1]	0.87	oz/week

Sources: 1. REPLACE trial Haak 2017; 2. Hayes 2013

  - Treatment Effects **(Table 2)**
    - **HbA1c**: Based on the real-world sensor data, the average number of scans per day (16) is associated with an HbA1c value that is 0.94% lower than the HbA1c value associated with the published average number of SMBG per day in this population (2.7/day, 8.1% HbA1c; Schutt 2005). See **Figure 1**.

Figure 1. Association between scan frequency and HbA1c



- **Non-severe hypoglycaemia:** a recent meta-analysis of T2DM patients using insulin was leveraged to establish the rate of minor hypoglycaemic events for the SMBG arm. Minor events are defined as hypoglycaemia not requiring third party assistance (Edridge 2015; proxied with events <70 mg/dL (ADA 2017)). The sensor data from the REPLACE trial for hypoglycaemic events under 70 mg/dl showed that after 6 months, FM was associated with a 27.7% reduction versus SMBG.
- **Major hypoglycaemia:** the REPLACE study was not powered to detect a difference in the rate of major hypoglycaemic events between the two arms and few events were seen. In the base case analysis, the rate of major hypoglycaemic events was assumed to be the same in both arms, using a rate from the published literature (Edridge 2015). Major events are defined as hypoglycaemic events requiring third party assistance (proxied with events <55 mg/dL (ADA 2017)).
  - In scenario analysis, the potential impact of more frequent scanning was explored based on the real-world data; this evidence suggests that 16 scans/day may lead to a median of 7.15% decrease in major (or "serious") hypoglycaemic events (SHE) of <55mg/dL (IQR: no difference, 11% decrease).
- **Utility Values**
  - A recent TTO study (Matza 2017) found a mean utility improvement of 0.03 (95% CI 0.023-0.038) associated with FM compared with SMBG.
  - Utility values (both for T2DM as well as complications) were obtained from the literature.
  - For NSHEs, the model leveraged the Lauridsen 2014 publication to employ a diminishing disutilities approach by calculating the disutility per event using the NSHE rate for each arm. The literature has shown that for the first few events, patients experience a higher disutility. As patients become more accustomed to having NSHEs, the disutility per event decreases.

Table 2. Key Model Inputs

Key inputs	FM	SMBG	Source
Physiological parameters			
Change from baseline HbA1c (IQR), % points	0.94 (0.72, 1.09)	0 (0, 0)	Dunn 2017
Adverse events			
Major hypoglycaemic events, per 100 patient-years*	105.00	105.00	Edridge 2015
Minor hypoglycaemic events, per 100 patient-years*	1,685.00	2,331.00	Edridge 2015, REPLACE trial
Utilities			
Annual utility score associated with treatment	0.03	0.00	Matza 2017
Baseline T2DM	0.785		Clarke 2002
Disutility for major hypoglycaemic event	-0.012		Currie 2006
Disutility for minor hypoglycaemic events	-0.0041	-0.0033	Calculated based on Lauridsen 2014
T2DM Intervention Costs			
Annual cost (year 1)	SEK 27,350	SEK 14,547	Calculation
Annual cost (year 2+)	SEK 25,923	SEK 14,547	Calculation
Key Acute Event Costs			
Minor hypoglycaemic event	SEK 0.00		Assumption
Major hypoglycaemic event	SEK 5,036		Jonsson 2006; Anderson 2002; DCCT 1991

"Major hypoglycaemic event" and "minor hypoglycaemic event" are the input labels used in the CDM v8.5
** Lower IQR was not associated with a difference in major hypoglycaemic events, and therefore only mean and upper IQR are tested in scenario analysis*

  - Costs & Resource Utilisation
    - Annual costs (2016 SEK) associated with managing T2DM were derived from public sources (medications, consumables) or the published literature (e.g. costs of complications). Intervention-specific costs reflect least expensive forms of consumables (pharmaceuticals and glucose monitor test strips) available from TLV, and the cost list from Skåne, Södra regionvårdnämnden 2015 informed physician fees.
    - Intervention-specific costs **(Table 2)** were calculated according to unit prices and trial-based resource utilisation, including:
      - FM Costs
        - » 26 sensors per year (1 every 2 weeks); 1 reader every 2 years;
        - » REPLACE trial resource use was applied: 109.5 back-up blood glucose test strips per year, 251.85 lancets per year, 85.2 units of insulin per day and one additional physician visit in the first year to ensure appropriate use of the device.
      - SMBG Costs
        - » REPLACE trial resource use: 1,095 strips per year, 459.9 lancets per year and 87.8 units of insulin per day.
  - Analyses
    - Total costs, effects, and an incremental cost-effectiveness ratio (ICER) were calculated for the base case analysis.
    - Scenario analyses were performed to explore the effect on HbA1c of the scan frequency interquartile range (approximately 10 and 20 scans/day for lower and upper IQR respectively), and the impact of scan frequency on hypoglycaemic event rates **(Table 3)** at base case and IQR scan levels (measured vs 55mg/dL event rate associated with scanning at same frequency as SMBG testers in literature).

Table 3: Scenario Analyses

Scenario	Description	Change in HbA1c (%)		Difference in rate of hypoglycemic events <55mg/dL (%)	
		FM	SMBG	FM	SMBG
Base case	HbA1c effect only (16 scans/day FM vs 5-6 scans/day SMBG)	-0.94%	0%	0%	0%
SA1	Adding SHE to base case HbA1c impact	-0.94%	0%	-7.15%	0%
SA2	Upper IQR, HbA1c effect only	-1.09%	0%	0%	0%
SA3	Upper IQR, HbA1c and SHE effects	-1.09%	0%	-11.00%	0%
SA4	Lower IQR, HbA1c effect only*	-0.72%	0%	0%	0%

**Note that lower IQR scan frequency showed no impact on major hypoglycaemic event rates, and therefore did not lead to additional scenario exploration*

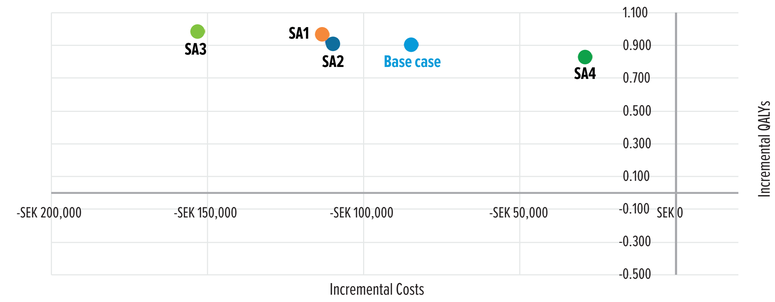
Results

- Base Case Analyses **(Table 4)**
  - The base case analysis shows FM use increases QALYs while saving costs.
    - With real-world FM sensor data indicating differential glucose testing frequency, this translated over the 40-year time horizon to 0.906 more QALYs attributable to lower HbA1c, fewer NSHEs, and the utility benefit associated with FM.
    - The incremental savings of FM versus SMBG (SEK 66,832 direct costs, and SEK 84,586 in combined direct and indirect costs) reflect the higher cost of the intervention, as well as reduced costs associated with managing downstream diabetes-related complications.
    - This implies that using FM may be considered a dominant strategy given the assumptions employed in this analysis.
- Scenario Analyses **(Figure 2)**
  - All scenarios continued to show cost savings with improved QALYs; results were therefore robust in the conclusion that FM may be dominant.

Table 4. Base Case Cost-Effectiveness Results

	FM	SMBG	Increment
LY	14.66	14.17	0.49
QALY	6.44	5.54	0.91
Direct Costs	SEK 1,472,625	SEK 1,539,457	-SEK 66,832
Combined Costs	SEK 1,966,052	SEK 2,050,638	-SEK 84,586
ICER (Direct SEK/QALY)		NA	Dominant
ICER (Combined SEK/QALY)		NA	Dominant

Figure 2. Scenario analyses



Limitations

- The main intervention effects in this study are based on cross-sectional real-world data.
  - Given the lack of baseline glucose data, it is not possible to establish a causal link between FM initiation and decrease in HbA1c.
  - However, the data do show a clearly higher average test frequency for FM patients (scanning 16x/day vs average 2.7x/day SMBG) and the associated average HbA1c is indeed lower for this population.
  - It remains valuable to understand that if FM leads to higher test frequency, the HbA1c effects and thus cost-effectiveness results will reflect those found in this analysis.
- It is not possible to determine patient characteristics associated with each reader in the real-world dataset.
  - The effects may be from a mixed Type 1 and Type 2 diabetes population.
  - There may be additional behavioural differences associated with frequent FM use, e.g. regarding adherence to dietary or medication plans that impact health outcomes.
  - This analysis therefore should be considered exploratory given use of mixed-population values together with trial-based T2DM characteristics.

Conclusion

- This exploratory analysis suggests that there may be HbA1c and hypoglycaemia effects that translate to long-term health and economic benefits due to higher glucose test frequency for patients using FM compared to SMBG.
- Given these benefits, FM may be considered cost-effective for T2DM patients receiving intensive insulin in Sweden.
- Based on the potential economic benefit seen in this exploratory analysis, future research should evaluate the real world FM test frequency in a T2DM population receiving intensive insulin, as well as demonstrate the longitudinal impact of changing test frequency.

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PMD75

Cost effectiveness analysis of a flash glucose monitoring system for Type 2 diabetes (T2DM) patients receiving intensive insulin treatment in Europe

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Background

- Type 2 diabetes (T2DM) is a chronic condition where the body develops a resistance to insulin, a hormone that promotes uptake of glucose from the bloodstream into cells where it is stored as an energy source for the body. As a result, the body produces more insulin to compensate but over time, sufficient amounts of insulin are unable to be produced. While lifestyle management interventions are initially recommended, patients will typically require pharmacologic interventions which can include insulin therapy. T2DM patients on intensive insulin therapy are recommended to frequently monitor their blood glucose level in order to administer the appropriate amount of insulin and alleviate symptoms of the disease and reduce the risk of long-term complications
- A novel, minimally-invasive flash glucose monitor (the FreeStyle Libre™ system, "FM") has been developed to continuously measure glucose levels from interstitial fluid using wired enzyme technology
  - The glucose level data are updated every minute and data are collected for 15-minute intervals and wirelessly transferred to a handheld reader with each scan of the sensor, which may be worn on the back of the upper arm for up to 14 days
  - The reader stores up to 90 days of data transferred 8 hours at a time, and provides glucose trends without requiring routine lancing and blood samples for self-monitoring of blood glucose (SMBG)
- In intensive insulin-treated T2DM patients, the REPLACE trial showed that using FM reduced the number of hypoglycaemic events and time spent in hypoglycaemia compared to using standard SMBG
- In addition, a recent time trade-off (TTO) study indicated utility improvement associated with FM (Matza 2015)
- However, the relative economic value of using FM vs. SMBG has not yet been evaluated with evidence from the recent trial

Objective

- To estimate the cost-effectiveness of using FM vs. SMBG through the IMS Core Diabetes Model (IMS CDM) for intensive insulin-treated T2DM patients in Europe, using Sweden as the core case, with additional results for Germany, Italy, France, and the Netherlands

Methods

- CDM Overview
  - The IMS CDM (v8.5), a non-product specific, multiplayer internet application to assess the long-term health outcomes and economic consequences for diabetes treatments, was used in this analysis. The IMS CDM has been published previously in detail, and its results have been validated against clinical and epidemiological studies (Palmer 2004, McEwan 2014). It has also been accepted as a valid model for use in health technology assessment (HTA) decisions (e.g. UK NICE DG 21, TA151, TA203, TA248, TA288, and TA336)
  - The IMS CDM combines Markov model structures and Monte Carlo simulation to capture major complications of diabetes and additional results including costs, life expectancy, and quality-adjusted life years (QALYs). Inputs include major and minor hypoglycaemic event rates and costs
  - For Sweden, the model utilized the Swedish NDR risk equation for HbA1c value prediction for T2DM (Kiadaliri 2013), while for other countries, the CDM default UKPDS risk equation was used. Other physiological parameters progressed according to data from the Framingham Heart Study (Wilson 1993)
- Analytic Overview
  - This analysis used version 8.5 of the CDM. A bootstrapping simulation approach was implemented for a 40 year time horizon with 1,000 simulation iterations containing 1,000 patients each; this approach was taken to create robust estimates and minimize Monte Carlo error
  - The simulation estimates direct costs, LYs, and QALYs over the time horizon, employing country-specific discount rates, with results reported in 2015 currency
  - For the core case, the analysis was conducted for T2DM patients in Sweden, where the study perspective is societal according to Sweden economic evaluation guidelines (Läkemedelsförmånsnämnden. Läkemedelsförmånsnämndens allmänna råd om ekonomiska utvärderingar 2003). Unit cost data as well as indirect data are from Sweden-specific publications and data sources
  - For other countries, perspectives reflect country-specific published guidance (payer or societal), and all country costs were obtained from public databases or published sources
- Model Inputs and Assumptions
  - Cohort Characteristics (**Table 1**)
    - The clinical trial population are those aged 18 years or over with poorly controlled T2DM and HbA1c of ≥7.5% (58 mmol/mol) and ≤12% treated by multiple daily injections of insulin or continuous subcutaneous insulin infusion for a minimum of 6 months (Clinical Study Report, REPLACE trial). Patients were using SMBG at least 10 times per week and were technically capable of using FM
    - The patient characteristics in the analyses reflect the REPLACE trial population; for inputs not available in REPLACE, published estimates were used

Table 1: Patients Characteristics

	Value (mean)	Units
Demographics[1]		
Start age	59.2	years
Duration of Diabetes	17.0	years
Male	67.0%	
Baseline risk factors		
HbA1c[1]	8.68%	

Sources: 1. REPLACE trial;

- Model Inputs and Assumptions
  - Treatment Effects (**Table 2**)
    - The REPLACE trial of patients with poor glycaemic control (N=242) showed that Hb1c decreased by 0.29% from baseline for the FM arm and by 0.31% in the SMBG arm
    - The rate of minor hypoglycaemic events for the SMBG arm was derived from a recent meta-analysis of T2DM patients, defined as a hypoglycaemic event not requiring third party assistance (Edridge 2015). The sensor readings for events under 70 mg/dl showed that after 6 months, FM reduced minor hypoglycaemic events by 27.7% compared to SMBG
    - The overall number of major hypoglycaemic events are assumed equal for both arms, with a rate derived from published literature (Edridge 2015). Major hypoglycaemic events were defined as an event requiring third party assistance
  - Utility Values (**Table 2**)
    - The TTO study found a mean utility improvement of 0.03 associated with FM (CI 95%: 0.023-0.038)
    - For NSHEs, the model leveraged the Lauridsen 2014 publication to employ a diminishing disutilities approach by calculating the disutility per event using the minor hypoglycaemic event rate for each arm. The literature has shown that patients experience higher disutility for the first events, with disutility per event decreasing over time

Table 2: Key Inputs in the Base Case

Key inputs	FM	SMBG	Source
Physiological parameters			
Change from baseline HbA1c (%-points)	-0.29 (0.78)	-0.31 (0.78)	REPLACE trial
Adverse events			
Major hypoglycaemic events (/100 patient-years)*	105.00	105.00	Edridge 2015
Minor hypoglycaemic events (/100 patient-years)*	1,685.00	2,331.00	Edridge 2015, REPLACE trial
Utilities			
Annual utility score associated with treatment	0.03	0.00	Matza 2015
Baseline T2D	0.785		Clarke 2002
Disutility for major hypoglycaemic event	-0.012		Currie 2006
Disutility for minor hypoglycaemic events	-0.0041	-0.0033	Calculated based on Lauridsen 2014
Indirect Costs			
Retirement age	65		OECD 2013
Age at first income	18		Assumption
Mean salary male (annual)	SEK 385,028.36		Statistics Sweden 2014
Mean salary female (annual)	SEK 331,052.43		Statistics Sweden 2014
No. work days/year	210		Ekonomifakta 2014

**"Major hypoglycaemic event" and "minor hypoglycaemic event" are the input labels used in the CDM*

- Model Inputs and Assumptions
  - Costs & Resource Utilization (**Table 3**)
    - All costs (2015 currency) are derived from national databases (medications, procedures) or the published literature (e.g. costs of complications), except for the FM intervention costs which is based on manufacturer data
    - Annual costs associated with managing T2DM were calculated based on country-specific unit prices and trial-based resource utilization, including:
      - FM Costs
        - » 26 sensors per year (1 every 2 weeks) in all countries except France (27 sensors). Local market assumptions of reader reimbursement were used
        - » REPLACE trial resource use was applied: 109.5 back-up blood glucose test strips per year, 251.85 lancets per year, 85.2 units of insulin per day and one additional physician visit in the first year (except for Germany where no additional physician visits were considered) to ensure appropriate use of the device
      - SMBG Costs
        - » REPLACE trial resource use was applied: 1,095 strips per year, 459.9 lancets per year and 87.8 units of insulin per day
- Scenario analyses were also performed to test the robustness of base case results (**Table 4**).

Table 3: Key Modeling and Cost Inputs

	SWE[1]	GER[1]	ITA[1]	FRA[1]	NL[1]
Modeling Considerations					
Perspective[2]	Societal	Statutory health insurance	Italian national health service	Collective national health insurance	Societal
Willingness to payICER/QALY threshold[3]	SEK330,000	€50,000*	€31,000-96,000	€30,000-90,000	€20,000-80,000
Discount Rate[2]					
Costs	3.00%	3.00%	3.00%	4.00%	4.00%
Clinical outcomes	3.00%	3.00%	3.00%	4.00%	1.50%
T2DM Intervention Costs					
Annual FM cost (year 1)	SEK25,517	€3,090	€3,068	€5,501	€2,764
Annual FM cost (year 2+)	SEK24,090	€3,090	€3,048	€5,465	€2,746
Annual SMBG cost (year 1+)	SEK14,547	€2,004	€2,274	€4,755	€1,731
Key Acute Events Costs[4]					
Major hypoglycaemic event	SEK5,036	€2,528	€1,391	€4,154	€3,343
Minor hypoglycaemic event	SEK0	€0	€0	€0	€0

Note: 1. SWE-Sweden, GER-Germany, ITA-Italy, FRA-France, NL-Netherlands; 2. Source by country: SWE- Läkemedelsförmånsnämnden. Läkemedelsförmånsnämndens allmänna råd om ekonomiska utvärderingar 2003; GER - IQWIG 2015; ITA-Capri 2001; FRA-Haute Autorité de Santé 2012; NL-Dutch Guidelines for Pharmacoeconomic Research 2006; 3. Source by country: SWE – Cleemput 2008, GER – Krejczy 2014, Neumann 2011, Merkesdal 2010; ITA- WHO 2015; FRA- Hamers 2012 and WHO 2015; NL-Simoens 2010; 4. Source by country:SWE- Jonsson et al 2006; Anderson et al 2002; DCCT 1991; GER-InEK 2013a; InEK 2013b; ITA-Allegato 1, Gazette Uffiziale, 2013; FRA- Torreton 2013; NL-Hammer 2009

**Hypothetical willingness to pay ICER/QALY threshold*

Table 4: Scenario Analyses Results

	Scenario	Description
1	Discount rate	Investigate impact of 0% discount rather than base case country-specific defaults
2	Time horizon	Explore shorter time horizons of 5 and 10 years
3	FM treatment utility	Vary treatment –related utility benefit in FM arm using the 95% CI (0.023 to 0.038)
4	Resource utilization - year 1	Vary the treatment cost associated with SMBG for year 1 only, given observed extra resource use from the clinical trial. Remove the cost of severe events to avoid double counting
5	Resource utilization - all years	Vary treatment cost associated with SMBG for all years, given observed extra resource use from the clinical trial. Remove the cost of severe events to avoid double counting
6	Subgroup: <65 years of age	Utilize cohort characteristics and treatment effects matching the <65 years of age population from the REPLACE trial

Results

- Base case analyses (**Table 5**)
  - For Sweden, the base case ICER (cost/QALY is SEK258,108), whereas the cost/minor hypoglycaemic event averted is SEK1,052
    - Over the 40-year time horizon, FM use led to higher QALYs due to fewer minor hypoglycaemic events and the utility benefit associated with the FM arm
    - The incremental cost of FM versus SMBG is largely attributed to the intervention cost in the base case
    - There were minor differences between the FM arm and the SMBG arm in terms of major complications, with slightly higher life expectancy produced in the SMBG arm due to the greater but not statistically different HbA1c reduction versus FM (-0.31% vs. -0.29%)
    - The ICER/QALY was well below the willingness to pay threshold of SEK 330,000
  - For other included countries, the base case scenario produces ICERs ranging from €20,097 (France), €20,968 (Italy), €21,105 (Netherlands) to €29,657 (Germany)
    - Results reflect a similar pattern to Sweden, with cost differences exclusively due to the FM system
  - All ICER estimations for these countries remain below published country-specific thresholds, suggesting that FM is cost-effective across countries

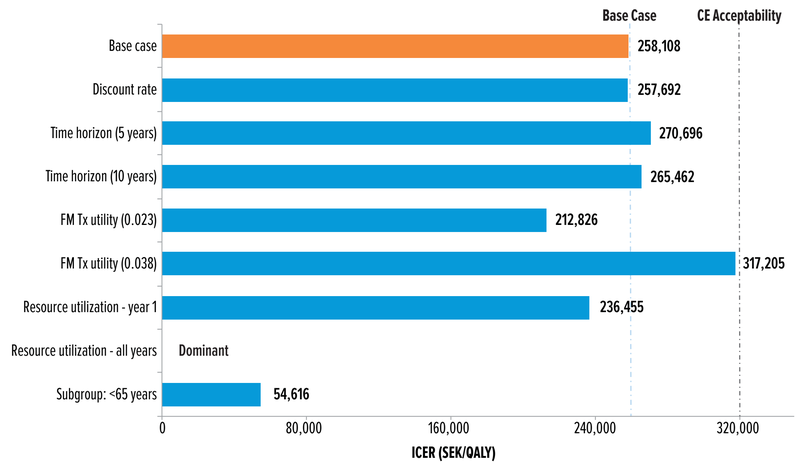
Table 5: Base Case Results

Country	FM Costs	FM LYs	FM QA-LYs	SMBG Costs	SMBG LYs	SMBG QA-LYs	Incremental Costs	Incremental LYs	Incremental QA-LYs	ICER/ QALY	Costs/ minor event-averted
Sweden*	SEK 2,108,292	14.33	6.21	SEK 1,963,932	14.34	5.65	SEK 144,360	-0.01	0.56	SEK 258,108	SEK 1,052
Germany*	€ 178,001	14.15	6.15	€ 151,900	14.16	5.61	€ 16,101	-0.01	0.54	€ 29,657	€ 119
Italy	€ 97,891	13.62	5.93	€ 86,822	13.61	5.40	€ 11,069	0.00	0.53	€ 20,968	€ 163
France	€ 161,687	12.39	5.50	€ 152,302	12.40	5.03	€ 9,385	0.00	0.47	€ 20,097	€ 164
Netherlands*	€ 185,177	16.56	7.11	€ 171,600	16.57	6.47	€ 13,577	-0.01	0.64	€ 21,105	€ 102

*Note: *Direct and indirect costs are included here*
NB: Country-specific survival curves lead to life year differences between countries

- Scenario analyses
  - For Sweden (**Figure 1**), among the scenario analyses performed, a 20% reduction in utility benefit had the largest impact on ICER in terms of SEK/QALY. In this case it rose to SEK317,205, yet remains below the Swedish threshold
  - When performing scenario analyses for the other countries, results reflect the same pattern as in Sweden; the largest impact on the ICER in terms of QALYs stems from a 20% reduction in utility benefit of FM

Figure 1. ICERs (base case and scenario analyses) for Sweden



Interpretation

- CDM
  - Although the CDM is well-validated, the impact of short-term outcomes associated with hypoglycemic events are not fully captured in the model and may be underestimated (NICE 2016)
    - The CDM assumes that minor hypoglycaemic events are not associated with the occurrence of severe events, although this has been shown in a recent study to be associated (Sreenan 2014)
    - The CDM does not incorporate the effects of hypoglycemic unawareness, which can increase the risk of experiencing major hypoglycemic events. Given how much previously unrecognised hypoglycaemia FM was able to detect in REPLACE, it may be that its use could help people avoid hypoglycaemic unawareness and thereby reduce risk of severe events
- Clinical
  - The main clinical data and patient characteristics for the analysis are taken from 6-month trials, and may not represent the real-world patient population or effects of FM. However, there were no trial protocol-mandated monitoring or adjustments to therapy, and therefore the results may be thought to approximate real-world use
- Inputs
  - Current utility values may underrepresent the quality-of-life impact of using FM.
    - The intervention-associated utility benefit, derived from a TTO study, assumed that FM offsets the need for blood tests performed on average 3 times per day by SMBG users. As some T2DM patients require 3 or more SMBG tests per day and given that FM users in the REPLACE trial scanned a mean of 8 times per day, the utility benefit for FM could be even greater
    - The disutility associated with minor (<70mg/dl) hypoglycaemic events is assumed to reflect the diminishing effect of each event as they become more frequent. However, this value is much smaller than that used in prior economic analyses (Currie et al 2006), and therefore, the ICERs in this study are likely to be conservative relative to other published values
- Given these considerations, there is potential for FM to be even more cost-effective than SMBG versus the analyses conducted

Conclusion

- This analysis of FM vs SMBG shows that improved hypoglycaemia outcomes and health utility benefit translate into economic value with incremental costs per QALY under published thresholds in Sweden, as well as in the other countries included in this analysis
- Results were robust in scenario analysis, and thus FM may be considered cost effective for use in T2DM patients receiving intensive insulin

Sponsored by Abbott Diabetes Care

Standardizing Clinically Meaningful Outcome Measures Beyond HbA_{1c} for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange

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OBJECTIVE

To identify and define clinically meaningful type 1 diabetes outcomes beyond hemoglobin A_{1c} (HbA_{1c}) based upon a review of the evidence, consensus from clinical experts, and input from researchers, people with type 1 diabetes, and industry. Priority outcomes include hypoglycemia, hyperglycemia, time in range, diabetic ketoacidosis (DKA), and patient-reported outcomes (PROs). While priority outcomes for type 1 and type 2 diabetes may overlap, type 1 diabetes was the focus of this work.

RESEARCH AND METHODS

A Steering Committee—comprising representatives from the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange—was the decision-making body for the Type 1 Diabetes Outcomes Program. Their work was informed by input from researchers, industry, and people with diabetes through Advisory Committees representing each stakeholder group. Stakeholder surveys were used to identify priority outcomes. The outcomes prioritized in the surveys were hypoglycemia, hyperglycemia, time in range, DKA, and PROs. To develop consensus on the definitions of these outcomes, the Steering Committee relied on published evidence, their clinical expertise, and feedback from the Advisory Committees.

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See accompanying articles, pp. 1611, 1614, 1631, 1641, 1644, 1651, and 1661.

RESULTS

The Steering Committee developed definitions for hypoglycemia, hyperglycemia, time in range, and DKA in type 1 diabetes. The definitions reflect their assessment of the outcome's short- and long-term clinical impact on people with type 1 diabetes. Knowledge gaps to be addressed by future research were identified. The Steering Committee discussed PROs and concluded that further type 1 diabetes–specific development is needed.

CONCLUSIONS

The Steering Committee recommends use of the defined clinically meaningful outcomes beyond HbA_{1c} in the research, development, and evaluation of type 1 diabetes therapies.

Type 1 diabetes is a life-threatening, autoimmune disease that strikes children and adults and can be fatal. People with type 1 diabetes have to test their blood glucose multiple times each day and dose insulin via injections or an infusion pump 24 h a day every day. Too much insulin can result in hypoglycemia, seizures, coma, or death. Hyperglycemia over time leads to kidney, heart, nerve, and eye damage. Even with diligent monitoring, the majority of people with type 1 diabetes do not achieve recommended target glucose levels. In the U.S., approximately one in five children and one in three adults meet hemoglobin A_{1c} (HbA_{1c}) targets and the average patient spends 7 h a day hyperglycemic and over 90 min hypoglycemic (1–3). The disease burden of type 1 diabetes can negatively impact quality of life, including finances and careers. In addition, the stress on and amount of time required of caregivers, including parents and children caring for aging parents living with type 1 diabetes, also burdens the entire family. There remains significant room for further improvement in the therapies and technologies designed to treat and assist in the management of this disease and prevent its life-threatening complications.

HbA_{1c} is a well-accepted surrogate outcome measure for evaluating the efficacy of diabetes therapies and technologies in clinical practice as well as in research (4–6). For the purposes of this article, the Steering Committee is using the Centers for Disease Control and Prevention's definition of population health outcomes, defined as a population's dynamic state of physical, mental, and social well-being (7). While HbA_{1c} is used as a primary outcome to assess glycemic control and as a surrogate for risk of developing complications, it has limitations. As a measure of mean blood glucose over 2 or 3 months, HbA_{1c} does not capture short-term variations in blood glucose or exposure to hypoglycemia and hyperglycemia in individuals with type 1 diabetes; HbA_{1c} also does not capture the impact of blood glucose variations on individuals' quality of life. Recent advances in type 1 diabetes technologies have made it feasible to assess the efficacy of therapies and technologies using a set of outcomes beyond HbA_{1c} and to expand definitions of outcomes such as hypoglycemia. While definitions for hypoglycemia in clinical care exist, they have not been standardized among organizations and there is inconsistency in the definitions used in different research studies. The lack of standard definitions impedes and can confuse their use in clinical practice, impedes development processes for new therapies, makes comparison of studies in the literature challenging, and may lead to regulatory and reimbursement decisions that fail to meet the needs of people with diabetes.

To address this vital issue, the type 1 diabetes–stakeholder community launched the Type 1 Diabetes Outcomes Program to develop consensus definitions for a set of priority outcomes for type 1 diabetes. A Steering Committee—comprising representatives from the American Association of Clinical Endocrinologists (AACE), the American Association of Diabetes Educators (AADE), the American Diabetes Association (ADA), the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society (PES), and the T1D Exchange—was the decision-making body for the Type 1 Diabetes Outcomes Program. The work of the Steering Committee was informed by diabetes researchers, industry, and people with diabetes through Advisory Committees representing each stakeholder group (Supplementary Data). The Steering Committee met for distinct in-person meetings in May and August 2016 to review the existing evidence and discuss and come to consensus on definitions for each priority outcome. Teleconferences and surveys of Advisory Committee members also informed discussions of outcome definitions. JDRF paid the expenses for this group, including teleconferences, travel expenses, and consulting services to facilitate group discussion, funded in part by a grant from The Leona M. and Harry B. Helmsley Charitable Trust. A draft consensus statement was posted on JDRF's website for 30 days in March 2017 to allow for public comments.

The outcomes prioritized under the program include hypoglycemia, hyperglycemia, time in range, diabetic ketoacidosis (DKA), and patient-reported outcomes (PROs). The Steering Committee, with input from the Advisory Committees, came to consensus on standardized definitions for each outcome based on published evidence and their expert opinion (or, in the case of PROs, a consensus that further type 1 diabetes–specific PRO development was needed). The focus for this program was type 1 diabetes, although the literature reviewed included data from people without diabetes and with type 2 diabetes to support the consensus statement. A parallel article published in this issue of *Diabetes Care* focuses more broadly on diabetes, and it is notable that the definitions reached are the same for both groups (8).

The immediate goal of the Type 1 Diabetes Outcomes Program was to identify and provide standardized definitions for an expanded set of clinical outcomes for research aimed at the development and evaluation of new diabetes therapies and technologies. It is not our expectation for any of the outcomes defined in this document to replace HbA_{1c}, as it remains an important outcome measure, but rather that they supplement its utility and allow for the capture of a more comprehensive understanding of how interventions might influence people with diabetes. The goal of the program is to ensure that defined outcomes are included as primary and secondary end points in type 1 diabetes research, development, and evaluation for future therapies.

For each outcome, the Steering Committee was asked to ensure that the consensus definition met the following criteria:

- Clinically meaningful
- Applicable to the nonpregnant population with type 1 diabetes
- Measurable using existing tools
- Applicable regardless of time of day (e.g., pre- and postprandial, day and night)

A summary of the consensus definitions is shown in Table 1, and a discussion of each outcome is provided in the following sections.

HYPOGLYCEMIA

Hypoglycemia is a significant—and potentially fatal—complication of type 1 diabetes management and has been found to be a barrier to achieving glycemic goals (9). Repeated exposure to severe hypoglycemic events has been associated with an increased risk of cardiovascular events and all-cause mortality in people with type 1 or type 2 diabetes (10,11). Hypoglycemia can also be fatal, and severe hypoglycemic events have been associated with increased mortality (12–14). In addition to the physical aspects of hypoglycemia, it can also have negative consequences on emotional status and quality of life.

While there is some variability in how and when individuals manifest symptoms of hypoglycemia, beginning at blood glucose levels <70 mg/dL (3.9 mmol/L) (which is at the low end of the typical postabsorptive plasma glucose range), the body begins to increase its secretion of counterregulatory hormones including glucagon, epinephrine, cortisol, and growth hormone. The release of these hormones can cause moderate autonomic effects, including but not limited to shaking, palpitations, sweating, and hunger (15). Individuals without diabetes do not typically experience dangerously low blood glucose levels because of counterregulatory hormonal regulation of glycemia (16). However, in individuals with type 1 diabetes, there is often a deficiency of the counterregulatory response, hindering their ability to avoid hypoglycemic events. Moreover, as people with diabetes experience an increased number of episodes of hypoglycemia, the risk of hypoglycemia unawareness, impaired glucose counterregulation (for example, in hypoglycemia-associated autonomic failure [17]), and level 2 and level 3 hypoglycemia (see DEFINITION under HYPOGLYCEMIA) all increase (18). Therefore, it is important to recognize and treat all hypoglycemic events in people with type 1 diabetes, particularly in populations (children, the elderly) that may not have the ability to recognize and self-treat hypoglycemia.

More notable clinical symptoms begin at blood glucose levels <54 mg/dL (3.0 mmol/L) (19,20). As the body's primary utilizer of glucose, the brain is particularly sensitive to decreases in blood glucose concentrations. Both experimental and clinical evidence has shown that, at these levels, neurogenic and neuroglycopenic symptoms including impairments in reaction times, information processing, psychomotor function, and executive function begin to emerge. These neurological symptoms correlate to altered brain activity in multiple brain areas including the prefrontal cortex and medial temporal lobe (21–24). At these levels, individuals may experience confusion, dizziness, blurred or double vision, tremors, and tingling sensations (25). Hypoglycemia at this glycemic level may also increase proinflammatory and prothrombotic markers (26). Left untreated, these symptoms can become severe to the point that an individual will require assistance from others to move or function. Prolonged untreated hypoglycemia that continues to drop below 50 mg/dL (2.8 mmol/L) increases the risk of seizures, coma, and death (27,28). Hypoglycemia that affects cognition and stamina may also increase the risk of accidents and falls, which is a particular concern for older adults with diabetes (29,30).

The glycemic thresholds at which these symptoms occur, as well as the severity with which they manifest themselves, may vary in individuals with type 1 diabetes depending on the number of hypoglycemic episodes they have experienced (31–33). Counterregulatory physiological responses may evolve in patients with type 1 diabetes who endure repeated hypoglycemia over time (34,35).

Definition

The Steering Committee defined three levels of hypoglycemia, as shown in Table 2. These levels are slight modifications to and will update the recently published ADA/EASD position statement (36).

Level 1

Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) that can alert a person to take action. A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a marker of physiological hypoglycemia in humans, as it approximates the glycemic threshold for neuroendocrine responses to falling glucose levels in individuals without diabetes. As such, blood glucose in individuals without diabetes is generally 70–100 mg/dL (3.9–5.6 mmol/L) upon waking and 70–140 mg/dL (3.9–7.8 mmol/L) after meals, and any excursions beyond those levels are typically countered with physiological controls (16,37). However, individuals with diabetes who have impaired or altered counterregulatory hormonal and neurological responses do not have the same internal regulation as individuals without diabetes to avoid dropping below 70 mg/dL (3.9 mmol/L) and becoming hypoglycemic. Recurrent episodes of hypoglycemia lead to increased hypoglycemia unawareness, which can become dangerous as individuals cease to experience symptoms of hypoglycemia, allowing their blood glucose levels to continue falling. Therefore, glucose levels <70 mg/dL (3.9 mmol/L) are clinically important, independent of the severity of acute symptoms.

Table 1—Summary of consensus definitions

Outcome	Definition
Hypoglycemia	Level 1: glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L) Level 2: glucose <54 mg/dL (3.0 mmol/L) Level 3: a severe event characterized by altered mental and/or physical status requiring assistance
Hyperglycemia	Level 1—elevated glucose: glucose >180 mg/dL (10 mmol/L) and glucose ≤250 mg/dL (13.9 mmol/L) Level 2—very elevated glucose: glucose >250 mg/dL (13.9 mmol/L)
Time in range	Percentage of readings in the range of 70–180 mg/dL (3.9–10.0 mmol/L) per unit of time
DKA	Elevated serum or urine ketones (greater than the upper limit of the normal range) and serum bicarbonate <15 mmol/L or blood pH <7.3

Table 2—Levels of hypoglycemia

Level	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance

Level 2

Level 2 hypoglycemia is defined as a measurable glucose concentration <54 mg/dL (3.0 mmol/L) that needs immediate action. At ~54 mg/dL (3.0 mmol/L), neurogenic and neuroglycopenic hypoglycemic symptoms begin to occur, ultimately leading to brain dysfunction at levels <50 mg/dL (2.8 mmol/L) (19,20). Neuroglycopenic symptoms—including behavioral changes, visual changes, seizure, and loss of consciousness—are the result of central nervous system neuronal glucose deprivation (21–23).

Level 3

Level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical status requiring assistance. Severe hypoglycemia captures events during which the symptoms associated with hypoglycemia impact a patient to such a degree that the patient requires assistance from others (27,28). Level 3 hypoglycemia is not mutually exclusive from level 1 or level 2. The Steering Committee considered it important to classify "altered mental and/or physical status requiring assistance" as its own category of hypoglycemia given that there are individuals who are able to function independently at a blood glucose <54 mg/dL (3.0 mmol/L) and therefore should not be grouped into the same category as those individuals who require third-party assistance. It is also important to include language on the need for third-party assistance as part of the definition for hypoglycemia, but the term "assistance" is subjective and needs to be clear to allow for evaluation. Including an "altered mental and/or physical status requiring assistance" clarifies the state that the individual is in when necessitating help to correct a low blood glucose value.

In addition to the glucose levels and signs included in the definitions, other specific signs or symptoms of hypoglycemia are important for consideration of individuals with hypoglycemia unawareness and variations in the presentation of hypoglycemia among different demographics. Hypoglycemia that sets in relatively rapidly, such as in the case of a significant insulin overdose, may induce level 2 or level 3 hypoglycemia with little warning (38).

Gaps in Evidence and Measurement

Currently, there is no consistent approach to collecting glucose data that would allow for the appropriate measurement of hypoglycemia. Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) are useful, but not perfect, and their results provide distinct information; one is a point-in-time measurement and the other is a continuous view into changes in glucose levels. Further, CGM can be useful for capturing hypoglycemia missed by SMBG, especially at night, and also for capturing time spent in hypoglycemia. The differences in the methodology and timing used for obtaining blood glucose readings are a challenge for interpreting clinical trial and real-world patient data. Given the differences in the outputs from SMBG and CGM, researchers and clinicians need to determine how the results are interpreted and when the blood glucose level requires a corrective action. The advent of additional information, including trending indicators on CGM devices (39), increases decision-making, as one must decide at what point to correct versus waiting for a low blood glucose to potentially increase. Additionally, there is no consensus on how long an individual must remain at a particular blood glucose level to be considered in the level 1 or level 2 hypoglycemic range (8). Much of the evidence on hypoglycemia to date has been obtained through conventional monitoring; the increased use of CGM and other technologies may provide more insights on these questions.

Therefore, new surveillance methods that provide consistent ways of reporting hypoglycemia should be developed to ensure adequate assessment of the impact of any intervention to prevent and treat the short-term effects of hypoglycemia, including the potential for death. More information on the impact of level 1 and level 2 hypoglycemia—both physiologically and with regard to impairment in how patients feel and function—is needed. Additionally, more work can be done on the links between level 1 and level 2 hypoglycemia to long-term outcomes, as well as the underlying factors of hypoglycemia-associated autonomic failure and other changes to physiological responses to repeated hypoglycemia over time.

HYPERGLYCEMIA

The Diabetes Control and Complications Trial (DCCT) proved that chronic hyperglycemia, as measured by a high HbA_{1c}, is a risk factor for microvascular complications, including retinopathy, nephropathy, and neuropathy (40). The DCCT follow-up study—Epidemiology of Diabetes Interventions and Complications (EDIC)—confirmed the findings of the DCCT and showed that chronic hyperglycemia also increases risk of nonfatal myocardial infarction, stroke, and death from cardiovascular disease (41). Other epidemiological evidence indicates that elevated blood glucose increases cardiovascular risk even in individuals without diabetes (42). The data regarding the effects of chronic hyperglycemia on long-term outcomes is conclusive, indicating that chronic hyperglycemia is a major contributor to morbidity and mortality in type 1 diabetes (41,43–45). The DCCT and subsequent studies have shown that intensive glucose management early in the life of people with type 1 diabetes can have long-lasting beneficial outcomes (46).

Although the correlation between long-term poor glucose control and type 1 diabetes complications is well established, the impact of short-term hyperglycemia is not as well understood. However, hyperglycemia has been shown to have physiological effects and in an acute-care setting is linked to morbidity and mortality in people with and without diabetes. Short-term hyperglycemia, regardless of diabetes diagnosis, has been shown to reduce survival rates among patients admitted to the hospital with stroke or myocardial infarction (47,48). In addition to increasing mortality, short-term hyperglycemia is correlated

with stroke severity and poststroke disability (49,50).

The effects of short-term hyperglycemia have also been observed in nonacute settings. Evidence indicates that hyperglycemia alters retinal cell firing through sensitization in patients with type 1 diabetes (51). This finding is consistent with similar findings showing increased oxygen consumption and blood flow in the retina during hyperglycemia. Because retinal cells absorb glucose through an insulin-independent process, they respond more strongly to increases in glucose in the blood than other cells in patients with type 1 diabetes. The effects of acute hyperglycemia on retinal response may underlie part of the development of retinopathy known to be a long-term complication of type 1 diabetes.

Reports of glucose profiles in individuals without diabetes may provide information to help define normal glucose ranges. For healthy individuals, data indicate that peak postmeal glucose values generally do not exceed 140 mg/dL (7.8 mmol/L) (52). However, other evidence indicates that the majority of individuals without diabetes have blood glucose values that exceed 140 mg/dL (7.8 mmol/L) every day (53,54). In one study, 93% of healthy participants spent time above 140 mg/dL (7.8 mmol/L) with median time above 140 mg/dL (7.8 mmol/L) at 26 min (range 0 min to 6 h 52 min) per day (53). This same study also found that nearly 10% of individuals without diabetes had blood glucose values that reach 200 mg/dL (11.1 mmol/L) during the day, which, by some standards, would be considered indicative of diabetes. Other studies suggest similar glucose patterns for individuals with normal glucose tolerance. A study in 32 individuals with confirmed normal glucose tolerance found that seven participants (22%) reached glucose concentrations >200 mg/dL (11.1 mmol/L) during an average of 28 days of CGM and that participants spent on average 42 min/day at glucose concentrations >140 mg/dL (7.8 mmol/L) (54). In contrast, glucose profiles for individuals with type 1 diabetes and type 2 diabetes demonstrated that glucose concentrations were >140 mg/dL (7.8 mmol/L) during ~60% of the total day or >180 mg/dL (10.0 mmol/L) during ~30% of the total day (52).

Pre- and postmeal glucose targets, approximating glycemic profiles of individuals without diabetes, are used in clinical practice to try to reduce exposure to hyperglycemia. Although specific goals are expected to vary based on individual needs, the ADA guidelines for individuals with diabetes (type 1 and type 2) indicate that premeal blood glucose should be between 80 and 130 mg/dL (4.4 and 7.2 mmol/L) and that peak postprandial glucose should be <180 mg/dL (10.0 mmol/L) (55). AACE guidelines for people with diabetes (type 1 and type 2) suggest that to achieve an HbA_{1c} of ≤6.5% (48 mmol/mol), premeal blood glucose may need to be <110 mg/dL (6.1 mmol/L) and 2-h postmeal blood glucose may need to be <140 mg/dL (7.8 mmol/L) (56,57). These levels represent ideal targets within a near-normal range, as a patient with diabetes may have large fluctuations in glucose levels in real time. All guidelines discuss the need to individualize therapy and create targets that are appropriate for each patient.

Definition

The Steering Committee defines hyperglycemia for individuals with type 1 diabetes as the following:

- Level 1—elevated glucose: glucose >180 mg/dL (10 mmol/L) and glucose ≤250 mg/dL (13.9 mmol/L)
- Level 2—very elevated glucose: glucose >250 mg/dL (13.9 mmol/L)

Level 1

Elevated glucose is defined as a glucose concentration >180 mg/dL (10.0 mmol/L) but ≤250 mg/dL (13.9 mmol/L). In clinical practice, measures of hyperglycemia differ based on time of day (e.g., pre- vs. postmeal). This program, however, focused on defining outcomes for use in product development that are universally applicable. Glucose profiles and postprandial blood glucose data for individuals without diabetes suggest that 140 mg/dL (7.8 mmol/L) is the appropriate threshold for defining hyperglycemia. However, data demonstrate that the majority of individuals without diabetes exceed this threshold every day. Moreover, people with diabetes spend >60% of their day above this threshold, which suggests that 140 mg/dL (7.8 mmol/L) is too low of a threshold for measuring hyperglycemia in individuals with diabetes. Current clinical guidelines for people with diabetes indicate that peak prandial glucose should not exceed 180 mg/dL (10.0 mmol/L). As such, the Steering Committee identified 180 mg/dL (10.0 mmol/L) as the initial threshold defining elevated glucose.

Level 2

Very elevated glucose is defined as a glucose concentration >250 mg/dL (13.9 mmol/L). Evidence examining the impact of hyperglycemia does not examine the incremental effects of increasing blood glucose. However, blood glucose values exceeding 250 mg/dL (13.9 mmol/L) increase the risk for DKA (58), and HbA_{1c} readings at that level have been associated with a high likelihood of complications.

Although hyperglycemia is often recognized at different levels depending on a number of circumstances, the above definition allows for the assessment of the ability of therapies and technologies to provide better glucose outcomes and to limit exposure to level 1 and level 2 hyperglycemic blood glucose values. The definition is meant to apply generally to people with type 1 diabetes at any given moment of the day. Further differentiating between blood glucose values >250 mg/dL (13.9 mmol/L) is less likely to be clinically meaningful except in instances of hyperglycemic hyperosmolar syndrome. For this reason, hyperglycemia is best defined with a two-category classification.

Gaps in Evidence and Measurement

Further research is needed to better understand the effects of individual episodes of hyperglycemia as opposed to sustained hyperglycemia over time. More research would be helpful for understanding the connections between hyperglycemia and macrovascular disease and other chronic complications, including the role of genetic factors and a patient's ability to recognize when hyperglycemia is occurring. This research is complicated by the fact that many patients with type 1 diabetes naturally have sustained hyperglycemia; CGM may benefit from such research. Also, more work can be done to elucidate any genetic variables that would affect physiological responses to hyperglycemia. PROs that address the impact of hyperglycemia for patients are also needed, as will be discussed in a later section.

TIME IN RANGE

An individual whose blood glucose levels rarely extend beyond the thresholds

defined for hypo- and hyperglycemia is less likely to be subject to the short-term or long-term effects experienced by those with frequent excursions beyond one or both thresholds. It is also evident that if the intent of a given intervention is to safely manage blood glucose but the intervention does not reliably maintain blood glucose within safe levels, then the intervention should not be considered effective.

The time in range outcome is distinguished from traditional HbA_{1c} testing in several ways (4,59). Time in range captures fluctuations in glucose levels continuously, whereas HbA_{1c} testing is done at static points in time, usually months apart (60). Furthermore, time in range is more specific and sensitive than traditional HbA_{1c} testing; for example, a treatment that addresses acute instances of hypo- or hyperglycemia may be detected in a time in range assessment but not necessarily in an HbA_{1c} assessment. As a percentage, time in range is also more likely to be comparable across patients than HbA_{1c} values, which are more likely to have patient-specific variations in significance (61). Finally, time in range may be more likely than HbA_{1c} levels to correlate with PROs, such as quality of life, because the outcome is more representative of the whole patient experience (62). Table 3 illustrates how the concept of time in range differs from current HbA_{1c} testing.

Nevertheless, evidence describing the negative effects of hypo- and hyperglycemia does not directly demonstrate the positive effects of maintaining blood glucose between those two thresholds. For example, evidence may point to health outcomes being optimal if time in range is defined at thresholds that are narrower than the hypo- and hyperglycemia thresholds. Also, variation in what is considered "normal" glucose fluctuations across populations, as well as what is realistically achievable for people with type 1 diabetes, must be taken into account so as not to make the target range definition too restrictive. In addition, as discussed in HYPERGLYCEMIA, clinical guidelines include pre- and post-meal glucose targets underscoring the importance of a target range.

At least one study has demonstrated the direct clinical relevance of time in range correlating to positive overall outcomes. This prospective inpatient study evaluated 227 patients (100 with type 2 diabetes and 127 without diabetes) post–cardiac surgery to assess glucose control. For the purposes of this study, time in range was defined as being time in the range of 108–146 mg/dL (6.0–8.1 mmol/L). Patients received insulin to target glucose concentrations within that range. The results of the study showed that post–cardiac surgery patients with 80% of time within a range of 108–146 mg/dL (6.0–8.1 mmol/L) had better outcomes, with or without diabetes, compared with patients with less than 80%. While the factors influencing inpatient recovery are varied, the study suggests a correlation between positive outcomes and time in range (63). Other research has indicated a link between a high percentage of time in range with recovery of glucose counterregulation and hypoglycemia symptom recognition in patients with type 1 diabetes following intrahepatic islet transplantation (64).

Table 3—HbA_{1c} testing and time in range outcome

HbA_{1c} testing	Time in range outcome
Evaluates single HbA_{1c} levels	Evaluates continuous glucose levels
Compares HbA_{1c} levels 3 months apart	May compare fluctuations for any given amount of time
Does not capture hypoglycemic or hyperglycemic levels occurring in the same day	Captures all glucose levels for the given time frame and identifies time within a safe range
Less likely to capture impact of acute interventions	Likely to capture impact of acute interventions

More commonly, time in range has been adopted by researchers evaluating the precision and effectiveness of emerging glucose monitoring and automated insulin delivery technologies. None of these studies relate time in range to any long-term diabetes outcomes, as these studies are of short duration. In one example, researchers compared a wearable, bihormonal, automated device to an insulin pump for 5 days over a 96-h period in 52 adults and adolescents with type 1 diabetes. Researchers measured the percent time in range by the hour, and the desired glucose range was defined as 70–180 mg/dL (3.9–10.0 mmol/L). They demonstrated that the bihormonal device was able to keep patients within a range of 70–180 mg/dL (3.9–10.0 mmol/L) for more time than the insulin pump, concluding that this device was a more effective means of managing blood glucose (65).

Definition

The Steering Committee defines time in range for individuals with type 1 diabetes as the following:

- Percentage of readings in the range of 70–180 mg/dL (3.9–10.0 mmol/L) per unit of time

The Steering Committee considered it important to keep the time in range definition wide in order to accommodate variations across the population with type 1 diabetes—including different age-groups—but limited enough to preclude the possibility of negative outcomes. The upper and lower bounds of the time in range definition are consistent with the definitions for hypo- and hyperglycemia defined above. For individuals without type 1 diabetes, 70–140 mg/dL (3.9–7.8 mmol/L) represents a normal glycemic range (66). However, spending most of the day in this range is not generally achievable for people with type 1 diabetes because they do not have physiological insulin secretion (67). The current postprandial blood glucose target for people with type 1 diabetes is 180 mg/dL (10.0 mmol/L), and, as such, an upper limit of 180 mg/dL (10.0 mmol/L) allows the definition to be applied across the broad population with type 1 diabetes (55).

The Steering Committee noted that, to date, the use of time in range has been to test the effectiveness of technologies designed to monitor blood glucose levels in real time and maintain glucose control. In order to generate the data necessary to measure time in range, CGM or similar technologies must be used. Use of CGM among the population with type 1 diabetes has been suggested to be ~11% in some populations and increasing in adoption rate (1). The Steering Committee felt that these technologies were at a point of development in which they could and should be used safely and effectively to capture time in range data.

Gaps in Evidence and Measurement

To date, there is limited research correlating time in range with positive short-term

and long-term type 1 diabetes outcomes, as opposed to the extensive research demonstrating the negative consequences of excursions into hyper- or hypoglycemia. More substantial evidence demonstrating a correlation or a direct causative relationship between time in range for patients with type 1 diabetes and positive health outcomes is needed.

Variations across the literature that examined time in range included differences in glycemic variability, dietary factors, sample sizes, and population demographics that will need to be reconciled as further research develops. A deficiency in evidence for the pediatric population was noted (67,68). Members of the committee noted that more evidence could be gathered on the experience of individuals with type 1 diabetes both in and out of glycemic range, which would potentially be captured in a PRO, as will be described later in this article.

DKA

DKA is often associated with hyperglycemia. In most cases, in an individual with diabetes, the cause of hyperglycemia is also the cause of DKA, although the two conditions are distinct. DKA develops when a lack of glucose in cells prompts the body to begin breaking down fatty acid reserves. This increases the levels of ketones in the body (ketosis) and causes a drop in blood pH (acidosis). At its most severe, DKA can cause cerebral edema, acute respiratory distress, thromboembolism, coma, and death (69,70).

The details of how DKA induces near-term physiological effects, as well as how it may potentially contribute to long-term complications, continue to be researched. Evidence suggests that DKA causes acute negative effects on the myocardium in adults and children, as indicated by increases of troponin I concentrations under DKA conditions (71).

DKA was found to be consistently characterized across studies. In part, this consistency was due to the well-known clinical effects of ketoacidosis, particularly low blood pH. Where definitions varied, the discrepancies are predominantly seen in minor changes to the range of what was considered mild or severe.

Definition

Although the current definition for DKA includes a list of multiple criteria that must be met, not all information currently included in the accepted definition is consistently gathered or required to diagnose DKA. The Steering Committee defines DKA in individuals with type 1 diabetes in a clinical setting as the following:

- Elevated serum or urine ketones (greater than the upper limit of the normal range), and
- Serum bicarbonate $<$15 mmol/L or blood pH $<$7.3

Given the seriousness of DKA, it is unnecessary to stratify DKA into different levels or categories, as the presence of DKA—regardless of the differences observed in the separate biochemical tests—should always be considered serious. In individuals with known diabetes, plasma glucose values are not necessary to diagnose DKA. Further, new therapeutic agents, specifically sodium–glucose cotransporter 2 inhibitors, have been linked to euglycemic DKA, or DKA with blood glucose values $<$250 mg/dL (13.9 mmol/L). Numerical values for urine or serum ketones are not specified in the DKA definition due to the variation in assay normal ranges across laboratory settings.

Gaps in Evidence and Measurement

DKA is a well-understood condition with well-recognized signs and symptoms. The current evidence is sufficient to support the definition described. Nevertheless, additional studies are needed to establish more definitive information about the effects of DKA and of recurrent DKA over time, including connections to vascular and cognitive complications. This limitation in research is likely due to studies of patients with DKA typically beginning only once patients are admitted to the hospital. There is also no evidence to suggest that there is a "safe" or benign amount of time to experience DKA; this may be a question worth exploring as, for example, varying degrees of DKA severity might have different long-term outcomes.

PROs

In guidance released in 2009 (72), the U.S. Food and Drug Administration (FDA) defined PROs as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." In the same document, the FDA clearly acknowledged the importance of PROs, advising that they be used to gather information that is "best known by the patient or best measured from the patient perspective."

Measuring and using PROs is increasingly seen as essential to evaluating care from a patient-centered perspective, which is a key aspect of health care reform efforts under the National Quality Strategy (73). PROs can capture information helpful for guiding diabetes care teams on which aspects of their care delivery they need to improve (74). Stakeholders have advocated for the inclusion of PROs as a component of a complete diabetes measure portfolio (75).

Given that type 1 diabetes is a chronic condition primarily treated on an outpatient basis, much of what people with type 1 diabetes experience is not captured through standard clinical measurement. Measures that capture PROs can fill these important information gaps. A variety of validated measures (including surveys and questionnaires) of some PROs for youth and adults with type 1 diabetes are available and are used in clinical studies, including those for diabetes distress (76) and fear of hypoglycemia (77). Work to further develop and validate tools and measures for diabetes health-related quality of life is ongoing.

Gaps in Measurement and Evidence

The use of validated PROs in type 1 diabetes clinical research is not currently widespread, and challenges to effectively measuring some PROs, such as quality of life, continue to confront researchers and developers. While many studies of type 1 diabetes treatments, including devices, in some way assess PROs (78,79), further work is needed to develop standard PROs for type 1 diabetes, including assessments of burden to patients. Such measures would need to be applicable across and between age ranges, settings, and over multiple years to evaluate trends in order to be relevant at the clinical trial level.

CONCLUSIONS

The Steering Committee developed definitions for outcomes beyond HbA_{1c} in type 1 diabetes including hypoglycemia, hyperglycemia, time in range, and DKA. These definitions were based on relevant published evidence and the clinical experience and expertise of the Steering Committee representatives and members of the Advisory Committees.

Knowledge gaps, including around PROs, were identified and should be addressed by future research. The Steering Committee recommends use of the defined clinically meaningful outcomes beyond HbA_{1c} in the research, development, and evaluation of type 1 diabetes therapies.

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Flash glucose monitoring in over 50,000 users: a favourable relationship between frequency of testing and glycaemic measures

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Background and aims: Optimising glycaemic control in diabetes involves a combination of reducing high glucose levels while avoiding hypoglycaemia. Our aim was to assess the use of flash glucose monitoring (FreeStyle Libre®) in real life clinical practice across European countries. In particular, glucose testing frequency and relationship with glycemic parameters was analysed together with regional differences in exposure to hyper and hypoglycaemia.
Materials and methods: When flash glucose readers are connected to an internet ready PC, 90-day memory of the device is de-identified and uploaded onto a database after user's consent. For analysis, sensors were required to have at least 120 hours of operation, and all sensors were grouped per reader, resulting in 50,831 readers with 279,446 sensors (86.4 million monitoring hours by 63.8 million scans). Six regions were identified, five countries having the highest device use (Germany, Spain, France, UK and Italy), and a sixth "region" grouped all remaining. Scan rate per reader was determined and twenty equally-sized rank-ordered groups, categorized by scan frequency, were evaluated. Glucose scan frequency was analysed together with relationship to glycaemic markers in each of these regions.
Results: Average scan frequency was 16.3/day [median (IQR) of 14 (10-20)] but this varied significantly across regions. Highest scan frequency was found in the UK at 18.0 [15 (11-23)] while individuals in France showed the lowest scan rate at 13.6 [12 (8-17); p<0.001]. All countries demonstrated strong correlations between frequency of glucose scans and glycaemic markers. Time spent in hyperglycemia (>10 mmol/l) was reduced from (mean±SD) 10.5±5 to 5.9±5 hours/day (p<0.001) in lowest compared with highest frequency scanning groups, while time in hypoglycaemia (<3.1 mmol/l) was reduced from 43±60 to 26±47 minutes/day (p<0.001). However, hypoglycaemic exposure showed regional differences with individuals in France spending the longest time in hypoglycaemia 58±65 to 40±62 minutes/day in lowest and highest frequency scanning groups, respectively, whereas patients from Italy spent the least time in hypoglycaemia 33±59 and 20±35 minutes/day in the lowest and highest frequency scanning groups. Increased scan frequency was also associated with longer time spent in range (defined as 3.9-10.0 mmol/l) and lower estimated HbA1c.
Conclusion: In real-world clinical practice, frequency of glucose testing with the flash monitoring system is high across countries, although regional differences were observed. Increased scan frequency is universally associated with reduced time spent in both hyper and hypoglycaemia but total exposure to low glucose levels showed differences between countries. These findings have implications for the use of flash glucose monitoring to improve glycaemia, whereas the documented regional differences warrant further research.
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Type 1 diabetes at high altitude: performance of medical devices

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Background and aims: High altitude trekking can expose people to extreme environmental conditions, like low temperatures and hypobaric hypoxia. Such extreme conditions make it more difficult for people with type 1 diabetes mellitus (T1DM) to achieve glycemic control. While frequent blood glucose monitoring is imperative in these cases, it remains unclear whether altitude impacts blood glucose meter accuracy. In this observational study, we examined the performance of various insulin pumps at high altitude, including continuous glucose monitoring (CGM) systems and a new flash glucose monitoring (FGM) system (FreeStyle Libre).
Materials and methods: All 19 patients with T1DM included in this study participated in trekking Damavand Mountain (Iran) to an altitude of 5671 meters above sea level. The mean age of the patients was 32.5 years, with a mean body mass index (BMI) of 23.8 kg/m^2, and a mean HbA_{1c} level of 6.6%.
Results: Statistical analysis showed a difference in blood glucose values obtained using the different glucose monitoring systems at day 1 (mean BGM values vs. mean FGM values, 137 vs. 169 mg/dl, p=0.0000), day 2 (mean CGM values vs. mean FGM values, 163 vs. 219 mg/dl, p=0.0014; and mean BGM vs. mean FGM values, 181 vs. 219 mg/dl, p=0.02), and day 3 (mean CGM values vs. mean FGM values, 202 vs. 264 mg/dl, p=0.0035; and BGM vs. FGM, 187 vs. 218 mg/dl, p=0.0000). The SmartGuard technology of insulin pump Minimed 640G (used by 6 patients during expedition) was activated on average 3.3 times per patient per day. We found that, without extreme weather conditions, high altitude trekking is safe for insulin pumps and CGM/FGM systems and causes no clinically significant problems. All pump models worked well without any disruption, and no cases of diabetes decompensation or severe hypoglycemia occurred.
Conclusion: To conclude, despite the risks, healthy, physically fit and experienced individuals with type 1 diabetes can be encouraged to participate in mountain trekking activities and attain their summit goals. Modern personal insulin pumps and continuous glucose monitoring systems appear to work properly even at high altitudes at least in the absence of extreme winter conditions.

Table 1. Glucose values during the three expedition days obtained via the different glucose monitoring methods

	Mean BGM values ± SD [mg dl]	Mean CGM values ± SD [mg dl]	Mean FGM values ± SD [mg dl]	Number of blood glucose measurements per day ± SD [mg dl]
Day 1 (3200–4200 m a s l)	153 ± 33	153 ± 19	168 ± 36	12.4 ± 4.3
Day 2 (4200–4700 m a s l)	183 ± 40	163 ± 19	219 ± 42	12.4 ± 6.4
Day 3 (4200–5671 m a s l)	202 ± 31	202 ± 30	264 ± 45	14.6 ± 7.6
P value	0.0004	0.0004	0.00005	0.48

BGM blood glucose measurement with a glucometer, CGM continuous glucose monitoring, FGM flash glucose monitoring

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Disclosure: **T. Klupa:** None.

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RESEARCH

Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis

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Abstract

Objectives To provide a systematic and quantitative summary of the association between severe hypoglycaemia and risk of cardiovascular disease in people with type 2 diabetes and to examine the sensitivity of the association to possible uncontrolled confounding by unmeasured comorbid severe illness using a bias analysis.

Design Meta-analysis of observational studies.

Data sources Medline, Embase, the Cochrane Library, and Web of Science databases were searched to February 2013, without any language restrictions.

Eligibility criteria Two independent reviewers selected cohort studies that evaluated the association of severe hypoglycaemia with cardiovascular events in people with type 2 diabetes; we excluded studies from acute hospital settings. We extracted descriptive and quantitative data.

Results Of 3443 citations screened, six eligible studies with 903 510 participants were identified. In the conventional random effects meta-analysis, severe hypoglycaemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05, 95% confidence interval 1.74 to 2.42; P<0.001). The excess fraction of cardiovascular disease incidence that was attributable to severe hypoglycaemia (the population attributable fraction) was 1.56% (95% confidence interval 1.32% to 1.81%; P<0.001). Although moderate heterogeneity across the studies was suggested (I^2=73.1%; P=0.002 for heterogeneity), most subgroups showed similar results in stratified analyses. The bias analysis indicated that comorbid severe illness alone may not explain the association between hypoglycaemia and cardiovascular disease; to explain this association, comorbid severe illness would have had to be extremely strongly associated with both severe hypoglycaemia and cardiovascular disease.

Conclusion Our findings suggest that severe hypoglycaemia is associated with a higher risk of cardiovascular disease; they also support the notion that avoiding severe hypoglycaemia may be important to prevent cardiovascular disease in people with type 2 diabetes.

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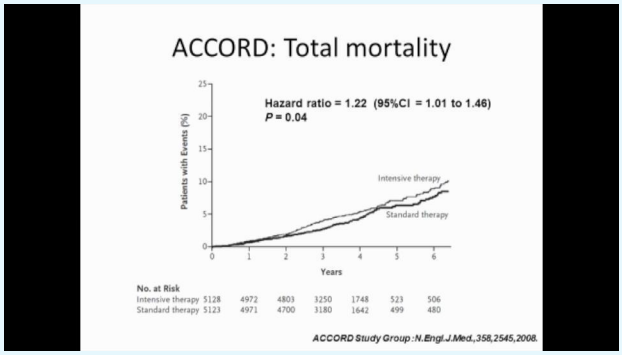

Video abstract

Introduction

Severe hypoglycaemia is a potential risk factor for cardiovascular disease in people with type 2 diabetes.[1 2] Meta-analyses of recent clinical trials indicated that intensive glucose control was associated with a reduced risk of non-fatal myocardial infarction in people with type 2 diabetes.[3 4] Individually, however, these recent clinical trials have failed to show a beneficial effect of intensive glucose control on overall cardiovascular disease events,[5-7] despite earlier observational studies indicating a strong positive association between diabetes or hyperglycaemia and risk of cardiovascular disease.[8-10] If severe hypoglycaemia induces cardiovascular disease events, it may also dilute the potential benefit of intensive glucose control on such events because intensive glucose control increases the risk of severe hypoglycaemia.[3] This is biologically plausible because severe hypoglycaemia has acute effects on sympathoadrenal activation,[11] inflammation,[12] and endothelial function,[13] all of which have potential adverse cardiovascular effects. In addition, cardiac ischaemia or fatal arrhythmia during hypoglycaemia may be responsible for the increased risk of cardiovascular disease among patients with severe hypoglycaemia.[14 15]

Although observational studies have reported a positive association between severe hypoglycaemia and risk of cardiovascular disease,[1 2] this association remains controversial. Some have suggested that severe hypoglycaemia may be a marker of vulnerability to cardiovascular disease events[1] because the risk of hypoglycaemia is increased in patients with comorbid severe illnesses (for example, renal disease, liver disease, cognitive decline, and terminal cancer) that are risk factors for serious adverse health outcomes. Thus comorbid severe illnesses may confound the association between hypoglycaemia and cardiovascular disease. Randomisation of patients to hypoglycaemic and non-hypoglycaemic groups is not feasible; however, a bias analysis may help to elucidate the impact of a comorbid severe illness on the association between severe hypoglycaemia and cardiovascular disease.

We conducted a systematic review and meta-analysis to evaluate if severe hypoglycaemia is associated with risk of cardiovascular disease, and if confounding from an unmeasured comorbid severe illness accounts for the reported association between severe hypoglycaemia and cardiovascular disease, using a bias analysis.

Methods

We searched Medline, Embase, the Cochrane library, and Web of Science to February 2013, without any language restrictions (initial search on 5 September 2012; search updated 11 December 2012 and 27 February 2013); a beginning timeframe was not set. The Medline search terms were ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) AND ("hypoglycemia"[MeSH Terms] OR "hypoglycemia"[All Fields] OR "hypoglycaemia"[All Fields]) AND ("cardiovascular diseases"[MeSH Terms] OR "cardiovascular diseases"[All Fields] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR ("cardiovascular"[All Fields] AND "disease"[All Fields])). We adapted this search strategy for searches of Embase (using Emtree terms), the Cochrane library, and the Web of Science (see supplementary text A). We also searched the references of relevant studies. Although this meta-analysis did not have a registered review protocol, we followed the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.[16] The researchers are experienced with systematic reviews of the literature.[17-22]

Study selection

Two independent investigators (AG and MG) read all retrieved abstracts and titles. The inclusion criteria were: a cohort study of people with type 2 diabetes, cardiovascular disease reported as the study outcome, and provision of an association between hypoglycaemia and cardiovascular disease. We defined cohort studies as those that prospectively identified a group of people, assessed exposures of interest, and followed them for incidence of outcome events (that is, prospective cohort studies) or those that used existing data records to retrospectively identify a group of people and assess exposures of interest and incidence of outcome events (that is, retrospective cohort studies). We included randomised controlled trials as long as an observational analysis of the association between hypoglycaemia and cardiovascular disease was available. Studies in acute hospital settings were excluded. Full texts of potentially eligible studies were retrieved and screened to determine their eligibility; discrepancies between the reviewers' selections were resolved by discussion.

Data extraction

We extracted information on study characteristics (authors, design, year of publication, sample size, duration of follow-up); participants' characteristics (age, sex, duration of diabetes, cardiovascular disease history, insulin use, body mass index, smoking status, low density cholesterol level, systolic blood pressure, glycated haemoglobin (HbA_{1c}) level, fasting plasma glucose level); exposure assessment; outcome assessment; analysis strategy; and multivariable adjusted relative risks. If the appropriate information was missing, we requested this from the investigators. Two investigators (AG and MG) extracted data independently and discrepancies were resolved by discussion.

Quality assessment

To assess study quality,[23] we evaluated each study for its design, sources of participants, follow-up time, exposure assessment, outcome assessment, and the extent of adjustment for potential confounders. We chose not to use a scoring system to formally rate study quality because such scoring submerges important information by combining disparate study characteristics into one score.[23]

Statistical analysis

We used relative risk as a measure of effect estimates. One study used logistic regression models to estimate odds ratios[24]; the others used Cox proportional hazard models to estimate hazard ratios.[1-27] Because the risk of cardiovascular disease incidence was low, we used both the hazard ratios and the odds ratios to approximate the relative risk.[23] We assessed potential publication bias using funnel plots, Begg's test,[28] and Egger's test.[29] We performed data synthesis using a conventional random effects model,[30] which ignores possible confounding by comorbid severe illness. We assessed statistical heterogeneity of relative risks across studies using the Cochrane's Q test[31] and I^2 statistics.[32] We considered low, moderate, and high degrees of heterogeneity to be I^2 values of below 25%, 25-75%, and above 75%, respectively. We also performed stratified analyses according to study design (that is, prospective studies[1 2] versus retrospective studies[24-27]), study location (United States[2-25] versus non-United States[1-27]), sex (mainly men[2 25] versus both sexes[1-27]),

duration of follow-up (>1 year[1-27] versus ≤1 year[24]), insulin use (included[1-27] versus excluded[26]), adjustment for race and dyslipidaemia (yes[2-27] versus no[1]), adjustment for smoking status (yes[1-25] versus no[24-27]), and adjustment for body mass index (yes[1 25] versus no[2-27]). We computed P values for comparisons between subgroups using the χ^2 test with 1 degree of freedom.

The potential impact of uncontrolled confounding by unmeasured severe comorbid illnesses was explored. Since data have not been published regarding the distribution of comorbid severe illnesses or their effect on the risk of cardiovascular disease in people with type 2 diabetes, we assigned a wide range of plausible bias values. We then computed the adjusted relative risks and 95% confidence intervals, externally adjusted for the unmeasured comorbid severe illnesses. Specifically, we conducted a bias analysis by dividing the observed (preadjusted) relative risk of each study (i=1, 2, etc) by a bias factor, which was interpreted as the degree of bias due to failure to adjust for severe comorbid illness, using the following formula[23 33]: bias factor$i$=$RR_{i\,\text{preadjusted}}/RR_{i\,\text{adjusted}}=(RR_{i\,DZ}P_{i\,Z1}+1-P_{i\,Z1})/(RR_{i\,DZ}P_{i\,Z0}+1-P_{i\,Z0})$ where $RR_{i\,\text{preadjusted}}$ is the observed relative risk; $RR_{i\,\text{adjusted}}$ is the relative risk adjusted for the unmeasured comorbid severe illness (Z); $RR_{i\,DZ}$ is the relative risk relating the unmeasured comorbid severe illness and cardiovascular disease (D), given hypoglycaemia; $P_{i\,Z1}$ is the prevalence of the unmeasured comorbid severe illness in the hypoglycaemic group; and $P_{i\,Z0}$ is the prevalence of the unmeasured comorbid severe illness in the non-hypoglycaemic group in each study (i=1, 2, etc).[23] The bias adjusted relative risk ($RR_{i\,\text{adjusted}}$), which was our target, was obtained by dividing the preadjusted relative risk ($RR_{i\,\text{preadjusted}}$) by the bias factor from the formula above. Although the degree of residual confounding may have differed across studies, we assigned the same bias factor to all studies for simplicity. Assuming that the standard errors of the bias adjusted relative risks were not affected by unmeasured confounding,[34 35] we estimated the standard errors of the logarithm of bias adjusted relative risks by the usual likelihood procedures. The bias adjusted relative risks were pooled using a random effects model.[30] We repeated the above adjustment process, using wide ranges of values, for the proportions of patients with comorbid severe illness and the effects of the comorbid severe illness on cardiovascular disease.

We also estimated the excess fraction of cardiovascular disease incidence that was attributable to severe hypoglycaemia (the population attributable fraction), under the assumption that the observed association of severe hypoglycaemia with cardiovascular disease risk represented a causal effect. To estimate the population attributable fraction (PAF), we used the following formula: $PAF=p_c(RR-1)/RR$, where p_c is the proportion of exposure prevalence among patients who developed cardiovascular disease.[23] We estimated p_c using the frequency of severe hypoglycaemia seen in patients who developed cardiovascular disease in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial; only this study provided the frequency in question (35/1147=3.1%). We estimated the confidence interval for the population attributable fraction using the Monte Carlo method.[36] The analyses were performed using SAS version 9.3 and Stata version 12.1.

Results

Our initial search identified 3443 citations. Based on the titles and abstracts, 56 citations were considered potentially eligible and we evaluated the full texts of these 56 citations. A total of 50 studies were subsequently excluded; three were performed in acute hospital settings, one was a design paper, 34 did not report an association between hypoglycaemia and cardiovascular disease, and 12 were reviews or abstracts from meetings. Of the three excluded studies performed in acute hospital settings, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI-2) study showed an association between hypoglycaemia and cardiovascular disease, but its study participants were patients admitted to participating coronary care units for suspected acute myocardial infarction.[37] Thus, the DIGAMI-2 study was not included in this meta-analysis. We did not include the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[38] or the study by McCoy et al[39]; these studies provided relative risks for mortality associated with hypoglycaemia, but the relative risk for cardiovascular disease associated with severe hypoglycaemia was not available. Of the meeting abstracts identified through our search, two satisfied our eligibility criteria[40 41]; the full text articles were retrieved[25 27] and included in our meta-analysis. Therefore, six studies were eventually included in the meta-analysis (fig 1⇓).[1-27]

Study characteristics and quality assessment

Tables 1⇓ and 2⇓ show the characteristics of the studies included in the meta-analysis. Two studies (the ADVANCE[1] study and the Veterans Affairs Diabetes Trial [VADT][2]) were secondary analyses of randomised clinical trials, and the other four studies (Johnston et al,[24] Zhao et al,[25] Rathmann et al,[26] and Hsu et al[27]) were based on administrative databases. The number of participants ranged from 1522 to 860 845, with a mean age range of 60-67 years and a mean duration of diabetes of 3.2-11.5 years; the follow-up period ranged from 1 to 5.6 years. The VADT,[2] Johnston et al,[24] and Zhao et al[25] studies were conducted in the United States; the ADVANCE study was done in Europe, Asia, Australia/New Zealand, and Canada[1]; Rathmann et al[26] in Germany; and Hsu et al[27] in Taiwan. The quality of the secondary analyses of randomised controlled trials (the ADVANCE study and VADT)[1 2] was generally high. The detailed quality assessment is described in supplementary text B and table A). All of the included studies adjusted for age, sex, history of cardiovascular disease, history of microvascular complications or its surrogate, baseline health status, and use of antihyperglycaemic agents. Other factors, such as race, dyslipidaemia, smoking status, and body mass index, were less consistently adjusted (table 2 and supplementary text). The impact of unmeasured comorbid severe illness was not assessed in these studies.

Conventional random effects meta-analysis

The six studies included 903 510 participants, with 1 to 5.6 years of follow-up. During the follow-up period, 0.6% to 5.8% experienced severe hypoglycaemia. The conventional random effects meta-analysis, which ignores unmeasured confounding, indicated that severe hypoglycaemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05, 95% confidence interval 1.74 to 2.42; P<0.001) (table 3⇓ and fig 2⇓). Moderate heterogeneity among these studies was indicated (I^2=73.1%; P=0.002 for heterogeneity). There was little evidence of publication bias. The funnel plot did not indicate asymmetry; Begg's P value was 0.71 and Egger's bias coefficient was 1.49 (95% confidence interval −1.50 to 4.47; P=0.24) (see supplementary figure A). We also estimated the population attributable fraction for cardiovascular disease associated with severe hypoglycaemia, assuming that the observed association between severe hypoglycaemia and cardiovascular disease reflected a causal effect of severe hypoglycaemia on risk of cardiovascular disease in people with

type 2 diabetes. The excess fraction of cardiovascular disease incidence attributable to severe hypoglycaemia was 1.56% (95% confidence interval 1.32% to 1.81%; P<0.001).

Stratified analysis

To examine possible sources of heterogeneity across studies, we carried out stratified analyses according to study design, study location, sex, duration of follow-up, insulin use, adjustment for race and dyslipidaemia, adjustment for smoking status, and adjustment for body mass index (table 3). Stratified analysis according to study design did not indicate apparent heterogeneity. Subgroups by duration of follow-up and by adjustment for race and dyslipidaemia seemed to differ in the magnitude of relative risk estimates. In a stratified analysis according to duration of follow-up, the pooled relative risk from studies with a duration of follow-up of more than one year[1-27] (that is, the pooled relative risk excluding the study by Johnston et al) was larger than the relative risk from the study by Johnston et al[24] (2.16, 95% confidence interval 1.77 to 2.64 *v* 1.79, 1.69 to 1.89; P=0.07 for interaction). In addition, the ADVANCE[1] study did not adjust for race and dyslipidaemia, and it had larger a relative risk than the pooled relative risk from the other studies[2-27] (3.45, 2.34 to 5.08 *v* 1.93, 1.70 to 2.18; P=0.005 for interaction). However, stratification by these factors did not explain much of the heterogeneity in results, with I^2 statistics moderate to high within each stratum.

Random effects meta-analysis with bias analysis

All studies showed a strong positive association between hypoglycaemia and cardiovascular disease (with point estimates of the relative risk ranging from 1.60 to 3.45). We performed a bias analysis to provide quantitative estimates, externally adjusted for comorbid severe illness (fig 3⇓ and supplementary table B). The bias analysis indicated that comorbid severe illness, alone, may not explain the observed association between severe hypoglycaemia and cardiovascular disease. To explain the association, comorbid severe illness would have had to be extremely strongly associated with both severe hypoglycaemia and cardiovascular disease. For example, to account for the association, comorbid severe illness would have needed to be 10 times more prevalent in patients with severe hypoglycaemia than in those without severe hypoglycaemia, and would have to have had a relative risk of 10.

Discussion

In this meta-analysis of 903 510 people with type 2 diabetes, we observed a higher risk of cardiovascular disease among those with severe hypoglycaemia. The bias analysis indicated that the observed association between severe hypoglycaemia and cardiovascular disease may not be entirely due to confounding by severe comorbid illness. Although moderate heterogeneity across the studies was indicated, most subgroups showed similar results in stratified analyses. The strength of association observed in the ADVANCE[1] study seemed to be greater than that in the other studies, possibly owing to differences in adjustment for potential confounding factors, study design, or study population; the strength of association in Johnston et al was lesser than that of the other studies, possibly because of its short duration of follow-up (one year). Given the concern that severe hypoglycaemia might be a risk factor for cardiovascular disease, avoiding severe hypoglycaemia may be important to prevent cardiovascular disease, and less stringent glycaemic targets may be considered for people with type 2 diabetes who are at high risk for hypoglycaemia. The findings provide additional support for the patient centred approach of the intervention for type 2 diabetes and glycaemic goal setting that aims to minimise the risk of hypoglycaemia, as recommended by the American Diabetes Association and the European Association for the Study of Diabetes.[42]

The association of severe hypoglycaemia with a higher risk of cardiovascular disease is biologically plausible. The sympathetic nervous response to severe hypoglycaemia increases catecholamine levels, resulting in acute adverse effects on the myocardium and the vascular system.[11] The increase in catecholamine also leads to platelet activation, leucocyte mobilisation, and coagulation,[12] which may trigger cardiovascular disease events. Inflammation and endothelial dysfunction are also induced by acute hypoglycaemia,[13] and both play roles in the development of atherosclerosis. Furthermore, cardiac ischaemia or fatal arrhythmia during hypoglycaemia may lead to cardiovascular disease.[14 15]

Strengths and limitations of this review

The strengths of this study include the large sample size and the use of bias analysis. This type of analysis has the advantage of quantitatively accounting for possible sources of bias.[43] Most published meta-analyses of observational studies do not explicitly and quantifiably evaluate those sources; instead, they are usually discussed in a more qualitative and abbreviated manner. However, when there are concerns that biases may be large, or when the observed associations seem precise, bias analyses can play an important role in drawing conclusions from these results.[43] We encourage the use of bias analysis in meta-analyses of observational studies, especially when performing risk assessments or determining policy implications. This meta-analysis also has several limitations. Firstly, the analysis was confined to published studies, and individual patient data were not available. Although the funnel plot, Begg's test, or Egger's test did not indicate publication bias, the possibility of bias remains. For example, the ACCORD trial was not included in our meta-analysis because the relative risk for cardiovascular disease associated with severe hypoglycaemia was not available. If the findings from the ACCORD trial become available, the pooled estimates need to be updated. Secondly, several additional biases are likely to exist. Selection bias may exist, especially in studies using data extracted from electronic medical records,[25] claims based databases,[24 27] or primary care databases.[26] Biases due to measurement error are also likely to be present, and may vary, in the included studies. The ICD-9-CM (international classification of diseases, ninth revision, clinical modification) or ICD-10 (international classification of diseases, 10th revision) coding may have led to outcome misclassification, biasing the results. Thirdly, there may also be other confounders, in addition to comorbid severe illness. A confounder, however, is required to have an effect substantially larger than the observed association and have a strong association with exposure,[23] and comorbid severe illness is the only such factor currently suggested. Fourthly, the outcomes included heterogeneous manifestations of cardiovascular disease. Severe hypoglycaemia may have affected the risk of one or more, but not of all, of the subcategories of cardiovascular disease; this may have diluted the effect of severe hypoglycaemia on cardiovascular disease, as a single category, in this meta-analysis. Fifthly, all of the included studies examined the association between hypoglycaemia and cardiovascular disease in secondary analyses. Thus future work should include well designed, prospective cohort studies with the primary intention of evaluating the association between

hypoglycaemia and risk of cardiovascular disease. Until then we believe that our results provide the best available evidence. Finally, our study was restricted to people with type 2 diabetes, which may limit the ability to generalise our findings to people with type 1 diabetes. Indeed, a recent study of relatively young people with type 1 diabetes found no association between severe hypoglycaemia and cardiovascular disease.[44] Although severe hypoglycaemia occurs more commonly in people with type 1 diabetes than those with type 2 diabetes, cardiovascular disease events are relatively rare among young people with type 1 diabetes.[44] Therefore, severe hypoglycaemia may have little impact on the risk of cardiovascular disease in these people.

Implications

Comorbid severe illness has been proposed to explain the positive association between severe hypoglycaemia and cardiovascular disease.[1] However, our bias analysis indicated that confounding due to comorbid severe illness is unlikely to explain the association. To explain this association, the prevalence of comorbid severe illness would have needed to be unrealistically high among patients who experienced severe hypoglycaemia, and the strength of the association between severe illness and cardiovascular disease would have needed to be extremely strong. Given that the observed association was already adjusted for a wide range of covariates, uncontrolled, residual severe illness in the individual studies was unlikely to be unequally distributed in this extreme fashion. Therefore, the present findings suggest that the association between severe hypoglycaemia and cardiovascular disease may not be entirely due to confounding by comorbid severe illness.

New recommendations for antihyperglycaemic therapy in non-pregnant adults with type 2 diabetes have recently been proposed by the American Diabetes Association and the European Association for the Study of Diabetes[42]; these recommendations emphasise individualisation of glycaemic goals. Because intensive glucose control increases the risk of severe hypoglycaemia,[3] the findings of this study add to the evidence supporting individualised glycaemic targets in people with type 2 diabetes.[42 45] Intensive therapy in the ACCORD trial was associated with a 22% increase in total mortality and a threefold increase in severe hypoglycaemia.[5] Furthermore, a subgroup analysis of the ACCORD trial indicated that the increased mortality associated with intensive therapy was limited to those with a glycated haemoglobin (HbA_{1c}) level of >8.0%,[5] suggesting that intensive glycaemic control may not be appropriate for those with poor glycaemic control. Our findings also support the notion that glucose lowering agents with a low propensity to induce hypoglycaemia (for example, metformin[46]) should be considered to avoid hypoglycaemia. Importantly, many severe hypoglycaemic episodes are preceded by a change in food intake,[47] suggesting that such episodes could be prevented by behavioural changes. In addition, particularly for patients treated with insulin, self monitoring of blood glucose can be useful in preventing hypoglycaemia.[48]

Conclusions

In summary, results from this meta-analysis suggest that severe hypoglycaemia is associated with approximately twice the risk of cardiovascular disease. Furthermore, a bias analysis indicates that the observed association between severe hypoglycaemia and cardiovascular disease may not be entirely due to confounding by comorbid severe illness. The findings support the notion that avoiding severe hypoglycaemia may be important to prevent cardiovascular disease in people with type 2 diabetes.

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Contributors: AG and MN designed the study. AG and MG independently searched the literature, selected the studies, and extracted the data. AG and OAA analysed and interpreted the data. AG and MG drafted the manuscript. OAA, YT, and MN contributed to the critical revision of the manuscript for important intellectual content. AG and NM are guarantors.

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Ethical approval: Not required.

Data sharing: No additional data available.

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What is already known on this topic

Earlier studies suggested a higher risk of cardiovascular disease in people with type 2 diabetes who experienced severe hypoglycaemia

The association is, however, controversial and some researchers have proposed that severe hypoglycaemia is merely a marker of comorbid severe illness

Moreover, a systematic and quantitative summary of published studies is not available

What this study adds

Conventional meta-analysis suggests that severe hypoglycaemia is associated with a higher risk of cardiovascular disease

Furthermore, a bias analysis indicates that comorbid severe illness alone may not entirely explain the positive association between severe hypoglycaemia and risk of cardiovascular disease

Avoiding severe hypoglycaemia may be important to prevent cardiovascular disease in people with type 2 diabetes

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Tables

Table 1| Characteristics of studies included in meta-analysis

Study (year of publication), location	Male (%)	Mean age (years)	Follow-up (years)	No of participants	Duration of diabetes (years)
ADVANCE (2010), Europe, Asia, Australia/New Zealand, Canada[1]	58	66	5.0 (median)	11 140	8 (mean)
VADT (2011), USA[2]	97	60	5.6 (median)	1791	11.5 (mean)
Johnston et al (2011), USA[24]	51	61	1.0 (mean)	860 845	NA
Zhao et al (2012), USA[25]	96	63	3.9 (median)	1522	NA
Rathmann et al (2012), Germany[26]	53	67	2.0 (mean)	25 712	3.2 (mean)
Hsu et al (2012), Taiwan[27]	47	65	2.8 (mean)	2500	3.8 (mean)

NA=not available.

Table 2| Exposures, outcomes, and adjustment for potential confounders of studies included in meta-analysis

Study	Exposure assessment	Outcome assessment	Adjustment for potential confounders
ADVANCE[1]	Hypoglycaemic episode that caused transient dysfunction of central nervous system and prevented patients from treating themselves (requiring help from someone else). 231 patients (2.1%) experienced severe hypoglycaemic episode	Death from cardiovascular cause, non-fatal myocardial infarction, or non-fatal stroke, which were validated by independent adjudication committee. Outcome occurred in 35 patients with hypoglycaemic episode (16.8%) and 1112 without hypoglycaemic episode (10.2%)	Age, sex, treatment assignment, duration of diabetes, history of macrovascular or microvascular complications, smoking status at baseline, and time dependent covariates during follow-up (age, glycated haemoglobin (HbA_{1c}), body mass index, creatinine levels, ratio of urinary albumin to creatinine, systolic blood pressure, and use of antihyperglycaemic agents or antihypertensive agents)
VADT[2]	Hypoglycaemic episode within previous three months that was life threatening or fatal, caused disability or incapacity, or required admission to hospital or medical intervention. 104 patients (5.8%) experienced severe hypoglycaemic episode	Myocardial infarction, cardiovascular death, cardiovascular accident, amputation due to ischaemia, surgical intervention for vascular disease, new or worsening congestive heart failure, stroke, and inoperable coronary artery disease that were adjudicated by an endpoints committee. Outcome occurred in 499 patients (27.9%)	Age, treatment assignment, duration of diabetes, previous cardiovascular event, insulin use, race, smoking status, and glycated haemoglobin (HbA_{1c}) at baseline. Time dependent covariates during follow-up included total cholesterol, high density lipoprotein cholesterol, and creatinine levels
Johnston et al[24]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-9-CM codes 251.0, 251.1, 251.2, and 250.8) using healthcare claims. 27 065 patients (3.1%) experienced hypoglycaemic episode	ICD-9-CM coded coronary artery bypass graft, revascularisation, percutaneous coronary intervention, acute myocardial infarction, or incidence of unstable angina, identified by healthcare claims. Outcome occurred in 5.3% of patients with hypoglycaemic episode and 2.2% without hypoglycaemic episode	Age, sex, location of residence, insurance type, Charlson comorbidity index, Agency for Healthcare and Research Quality comorbidity index, hypercholesterolaemia, hypertension, peripheral vascular disease, chronic kidney disease, baseline microvascular complications, baseline medical expenditures, number of medical encounters with diagnosis of diabetes, previous cardiovascular disease, and use of antihyperglycaemic, antiplatelet, antihypertensive, or anticoagulant agents
Zhao et al[25]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-9-CM codes 251.0, 251.1, 251.2, and 250.8) using data from electronic medical records. 761 patients (1.7%) experienced hypoglycaemic episode	ICD-9-CM coded myocardial infarction, stroke, congestive heart failure, and peripheral vascular disease identified by data from electronic medical records. Outcome occurred in 30.65% patients with hypoglycaemic episode and 17.48% without hypoglycaemic episode	Age, sex, race, marital status, body mass index, insurance, renal disease, mental disorder, substance misuse, tobacco use, Charlson comorbidity index, and use of antihyperglycaemic agents, antihypertensive agents, or statins
Rathmann et al[26]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-10 codes E16.0, E16.1 and E16.2) using primary care databases. Hypoglycaemic episode documented in 0.7% of patients	ICD-10 coded coronary heart disease, myocardial infarction, stroke, and peripheral vascular disease, identified by data from primary care databases. Outcome occurred in 12.5% of patients	Age, sex, location of residence, insurance type, practice (diabetologist), Charlson comorbidity index, hyperlipidaemia, hypertension, baseline microvascular complications, and use of antihyperglycaemic, antihypertensive, lipid lowering, or antithrombotic agents
Hsu et al[27]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-9-CM codes 251.2×) using inpatient claims. Hypoglycaemic episode documented in 0.6% of patients	ICD-9-CM coded cardiovascular diseases (ICD-9-CM codes 390 to 459) from hospital claim dataset. Outcome occurred in 106/1000 person years in patients without hypoglycaemic episode and 324/1000 person years in patients with hypoglycaemic episode	Age, sex, duration of diabetes, dyslipidaemia, hypertension, atrial fibrillation, liver cirrhosis, renal disease, mental disease, previous cancer, previous stroke, previous heart disease, high social economic status, good compliance, and use of antihyperglycaemic agents

Table 3| Stratified analysis of severe hypoglycaemia and risk of cardiovascular disease

Group	No of studies	Relative risk* (95% CI)	P for heterogeneity†	I^2 (%)	P for interaction‡
Total	6	2.05 (1.74 to 2.42)	0.002	73.1	
Design:					
Prospective	2	2.67 (1.48 to 4.80)	0.10	63.8	0.29
Retrospective	4	1.93 (1.68 to 2.21)	0.03	65.4	
Study location:					
USA	3	1.81 (1.71 to 1.90)	0.58	0.0	0.18
Non-USA	3	2.29 (1.62 to 3.24)	0.02	76.2	
Sex:					
Men (>95%)	2	1.99 (1.64 to 2.41)	0.85	0	0.71
Both	4	2.10 (1.67 to 2.65)	<0.001	83.4	
Follow-up (years):					
>1	5	2.16 (1.77 to 2.64)	0.048	58.2	0.07
≤1	1	1.79 (1.69 to 1.89)	—	—	
Insulin users:					
Included	5	2.13 (1.77 to 2.57)	0.001	77.6	0.15
Excluded	1	1.60 (1.13 to 2.26)	—	—	
Adjustment for race and dyslipidaemia:					
Yes	5	1.93 (1.70 to 2.18)	0.07	53.9	0.005
No	1	3.45 (2.34 to 5.08)	—	—	
Adjustment for smoking status:					
Yes	3	2.37 (1.61 to 3.47)	0.043	68.2	0.32
No	3	1.91 (1.59 to 2.29)	0.02	75.0	
Adjustment for body mass index:					
Yes	2	2.56 (1.50 to 4.36)	0.01	83.3	0.30
No	4	1.91 (1.62 to 2.34)	0.046	62.5	

*Relative risk estimates obtained using conventional random effects model.

†P values for heterogeneity across studies computed using Cochrane's Q test.

‡P values for comparisons between subgroups computed using χ^2 test with 1 degree of freedom.

Figures

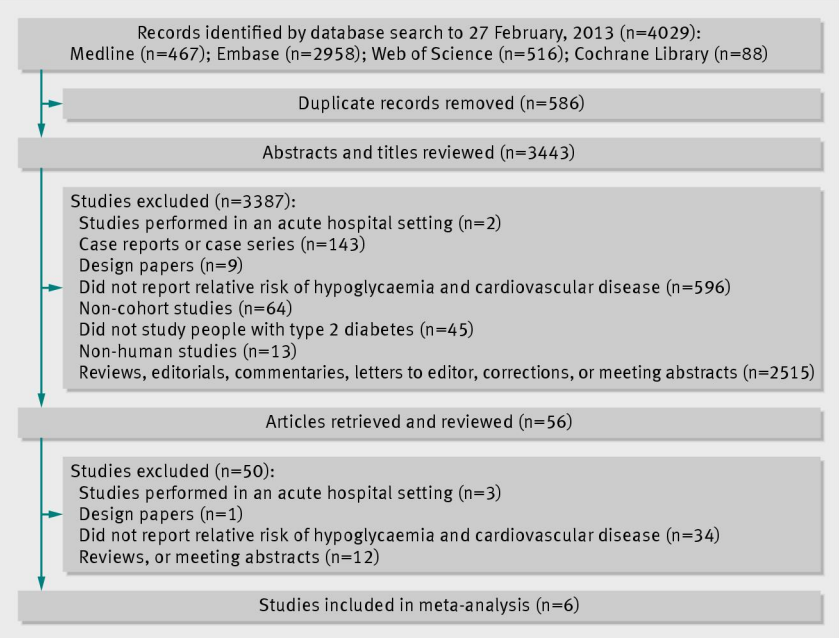

Fig 1 Flow of studies through review

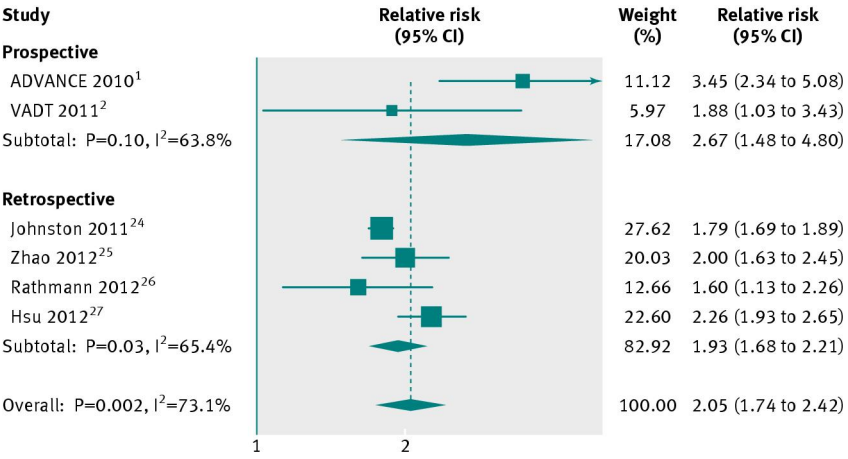

Fig 2 Conventional random effects meta-analysis according to study design. ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT=Veterans Affairs Diabetes Trial. Dots indicate relative risks for severe hypoglycaemia and cardiovascular events in people with type 2 diabetes. Horizontal lines indicate 95% confidence intervals for relative risks. Diamonds represent pooled relative risk estimates with 95% confidence intervals

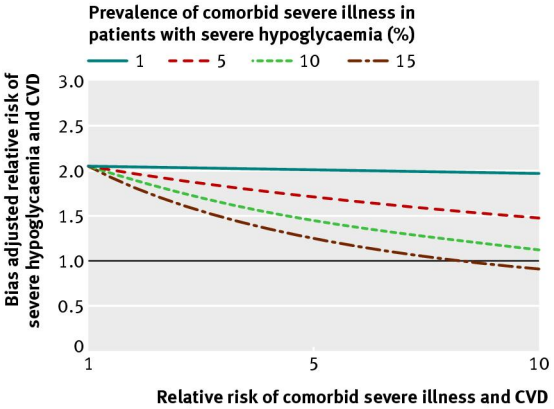

Fig 3 Random effects meta-analysis with bias analysis. Bias adjusted relative risks of severe hypoglycaemia and cardiovascular disease were computed to examine the sensitivity of the association to possible confounding by comorbid severe illness. The prevalence of comorbid severe illness in patients without severe hypoglycaemia was assumed to be 0.5%. CVD=cardiovascular disease

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ORIGINAL RESEARCH

Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes

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ABSTRACT

Introduction: Published evaluations of sensor glucose monitoring use in insulin treated type 2 diabetes are limited. The aim of this study was to assess the impact of flash glucose-sensing technology as a replacement for self-monitoring of blood glucose (SMBG) over a 12-month period in participants with type 2 diabetes who were on intensive insulin therapy.

Methods: An open-label, randomized, controlled study in adults with type 2 diabetes on intensive insulin therapy from 26 European diabetes centers aimed at assessing flash glucose sensing technology was conducted. Participants ($N = 224$) were randomized (1:2 respectively) to a control group ($n = 75$) that used SMBG (FreeStyle Lite™) or to an intervention group ($n = 149$) which used sensor glucose data (FreeStyle Libre™ Flash Glucose Monitoring System) for self-management over 6 months. All intervention group participants who completed the 6-month treatment phase continued into an additional 6-month open-access phase.

Results: A total of 139 intervention participants completed the 6-month treatment phase and continued into the open-access phase. At 12 months (end of open-access period), time in hypoglycemia [sensor glucose <3.9 mmol/L (70 mg/dL)] was reduced by 50% compared to baseline [−0.70 ± 1.85/24 h (mean ± standard deviation); $p = 0.0002$]. Nocturnal hypoglycemia [2300 to 0600 hours, <3.9 mmol/L

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(70 mg/dL)] was reduced by 52%; $p = 0.0002$. There was no change in time in range [sensor glucose 3.9–10.0 mmol/L (70–180 mg/dL)]. SMBG testing fell from a mean of 3.9 (median 3.9) times/day at baseline to 0.2 (0.0), with an average frequency of sensor scanning of 7.1 (5.7) times/day at 12 months, and mean sensor utilization was 83.6 ± 13.8% (median 88.3%) during the open-access phase. During this 6-month extension period no device-related serious adverse events were reported. Nine participants reported 16 instances of device-related adverse events (e.g. infection, allergy) and 28 participants (20.1%) experienced 134 occurrences of anticipated skin symptoms/sensor-insertion events expected with device use (e.g. erythema, itching and rash).

Conclusion: The use of flash glucose-sensing technology for glycemic management in individuals with type 2 diabetes treated by intensive insulin therapy over 12 months was associated with a sustained reduction in hypoglycemia and safely and effectively replaced SMBG.

Trial Registration: ClinicalTrials.gov identifier, NCT02082184.

Keywords: Flash sensor glucose technology; Glucose monitoring; Insulin; Type 2 diabetes

INTRODUCTION

The management of hyperglycemia remains a primary focus of diabetes management in patients with type 2 diabetes. Current management strategies balance optimization of glucose control with potential risks from the therapy, especially hypoglycemia [1]. In both type 1 and type 2 diabetes, increased hypoglycemic risk is associated with the duration of diabetes and insulin use [2, 3] and not with glycated hemoglobin (HbA1c) level [3]. Prandial insulin carries a higher risk for non-severe hypoglycemia than treatment with basal insulin alone [4], and intensive insulin treatment for the management of type 2 diabetes further increases the risk for severe hypoglycemia [5]. Therefore, enhanced detection of dysglycemia for patients with type 2 diabetes managed with multiple daily injections or continuous subcutaneous insulin infusion (CSII) is essential and can be challenging with self-monitoring of blood glucose (SMBG) as neither hypo- nor hyperglycemia are easily detected [6]. Continuous glucose monitoring (CGM) can offer enhanced assessment of glycemic issues; however, current guidance for CGM use and benefit in the patient population with type 2 diabetes excludes the use of intensive insulin therapy [7] due to the scarcity of published data in this population [8].

Our results from the randomized controlled trial "Novel Glucose-sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-treated Type 2 Diabetes (REPLACE)", which compared the safety and efficacy of the new flash glucose-sensing technology to SMBG over a 6-month period have been published [9]. This study included an additional 6-month open-access phase for all participants in the intervention group. The aim of the open-access phase was twofold: to evaluate (1) the safety of the new device in day-to-day use over an extended time period by assessing changes in glycemic measures between baseline and 12 months and (2) device-related adverse events.

The flash glucose-sensing technology used was FreeStyle Libre™, a sensor-based flash glucose monitoring system (Abbott Diabetes Care, Witney, UK). This small, single-use, factory-calibrated, on-body sensor utilizes wired enzyme technology (osmium mediator and glucose oxidase enzyme co-immobilized on electrochemical sensor) to continuously monitor interstitial glucose levels. The sensor is worn on the back of the arm for up to 14 days and automatically stores glucose data every 15 min. A real-time glucose level may be obtained as often as each minute by scanning the sensor with the reader. A glucose trend arrow (indicating rate and direction of change in glucose levels) and a graphical trace of glucose values for the previous 8-h period is also displayed on the screen. Data are transferred wirelessly by radio frequency identification from the sensor to the reader memory which stores historical sensor data for 90 days. Data can be uploaded using the device software to generate summary glucose reports (including an ambulatory glucose

profile) for review by the patient at home or in the clinic with their healthcare professional [10].

METHODS

Details on the rationale, methodology and results of the treatment phase (6 months) of the REPLACE study have been described previously [9]. Briefly, this was a 6-month, prospective, open-label, non-masked, two-arm, randomized controlled study that was conducted at 26 European diabetes centers (8 in France, 10 in Germany, 8 in the UK). The treatment phase of the study was designed to compare the use of novel flash glucose sensing technology with SMBG in participants with type 2 diabetes treated with multi-dose insulin therapy. Following completion of the 6-month treatment phase, intervention group participants continued using flash sensing technology for a further 6 months during the open-access period.

At each study center, any potentially eligible patient from the general diabetes population was invited to participate in the study if they were ≥18 years of age with type 2 diabetes treated with insulin for at least 6 months and on their current regimen (prandial only or prandial and basal multi-dose-insulin therapy or CSII therapy) for ≥3 months; had an HbA1c level of 58–108 mmol/mol (7.5–12.0%); had self-reported regular blood glucose testing data (more than 10/week for at least 2 months prior to study entry); were considered by the investigator to be technically capable of using the flash sensor-based glucose monitoring system.

Participants were not included for the following reasons: if they had any other insulin regimen to that described above; had a total daily dose of insulin ≥1.75 U/kg on study entry; had severe hypoglycemia (requiring third-party assistance) [8], diabetic ketoacidosis or hyperosmolar–hyperglycemic state in the preceding 6 months; had a known allergy to medical-grade adhesives; used continuous glucose monitoring within the previous 4 months; were pregnant or planning pregnancy; were receiving steroid therapy for any condition; were considered by the investigator to be unsuitable to participate.

Approval was given by the appropriate competent authorities in each country. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for participation in the study.

Following 2 weeks of blinded sensor wear, the subjects were randomized (centrally, using biased-coin minimization dependent on study center and insulin administration) to the control group (SMBG) or to the intervention group (glucose-sensing technology). For the 6-month treatment phase (post-randomization), the sensor-based glucose monitoring system was un-blinded for the participants in the intervention group so that they could continuously use sensor glucose data for self-management, including insulin dose decisions, in accordance with the product labeling. No training was provided to these participants for interpretation of glucose sensor data. Their historical data was uploaded at subsequent study visits, and glucose reports [including ambulatory profile reports (AGP)] were generated for review by the healthcare professional with the participant, using the device software [10].

At 6 months (day 208), all control participants concluded their involvement in the study while intervention participants entered an open-label, open-access study phase for a further 6 months. For the open-access phase participants continued to use the sensor-based glucose monitoring system for their day-to-day glucose management and also to record any events in their event diary. These participants had a review of their glucose reports with the clinician at 3-month intervals; at the beginning of the open-access phase and after a further 3 months (day 284). Similar to the visits during the intervention phase, at these visits the effect of life-style/diet on glucose levels and insulin doses were discussed and any management changes agreed upon. In order to continue to reflect "real world" conditions there was no pre-set algorithm for insulin adjustments mandated by the protocol. However, common principles continued to be applied, including

avoidance of hypoglycemia, optimization of fasting glucose and reduction of postprandial glucose excursions.

Outcomes

The primary outcomes were changes in sensor-derived glycemic measures between baseline and 12 months post-baseline. The sensor-derived glycemic measures were number and duration of hypoglycemic events [glucose <3.9 mmol/L (70 mg/dL)] and number and duration of hyperglycemic events [glucose >13.3 mmol/L (240 mg/dL)].

Pre-specified secondary endpoints included sensor-derived glycemic measures between baseline and 12 months post-baseline; frequency of glucose finger-sticks and sensor scans per day during the study period; and total daily dose of insulin. Sensor-derived glycemic measures included number and duration of hypoglycemic events [glucose <3.1 mmol/L (55 mg/dL)]; time in glucose range 3.9–10.0 mmol/L (70–180 mg/dL), number and duration of hyperglycemic events [glucose >10.0 mmol/L (180 mg/dL)]; mean and standard deviation (SD) glucose. An event was defined as at least two consecutive readings, at 15-min intervals, outside the predefined glucose range (the end of an episode was 1 reading at or inside the predefined range).

Safety endpoints incorporated all adverse events, including severe hypoglycemia (requiring third-party assistance [2]), hypoglycemic events and sensor insertion or sensor wear-related symptoms, diabetic ketoacidosis or hyperosmolar hyperglycemic state episodes and cardiac events.

Statistical Analysis

Differences between post-baseline and baseline measurements were evaluated using a paired *t* test. Sensor-derived glycemic endpoint values were excluded from the analysis if <72 h of sensor results were available from the final 14-day sensor wear (days 374–388). Confidence intervals were calculated for the mean difference from baseline.

The results presented here are for the full analysis set. Data analysis was performed by a contract research organization (ICON PLC; Dublin, Ireland, managed by Abbott Diabetes Care) and by Abbott Diabetes Care. We used SAS version 9.2 or higher for all analyses (SAS Institute, Cary, NC).

The trial is registered with ClinicalTrials.gov, number NCT02082184.

RESULTS

All 139 (100%) intervention participants completing the treatment phase continued into the open-access phase, of whom 125 completed the open-access phase (Fig. 1). The primary reason for discontinuation was skin reaction at the sensor site. Participants' baseline characteristics are summarized in Table 1. Sensor-derived glycemic endpoint values were included for 108 participants who had ≥72 h of sensor results

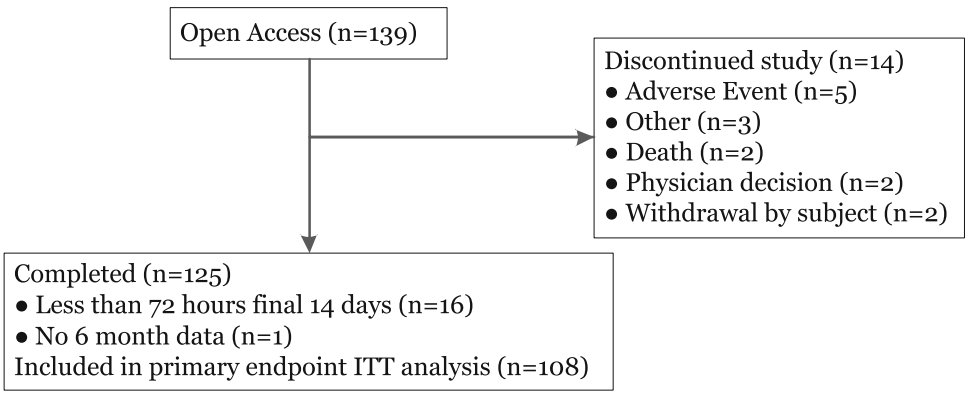

Fig. 1 Trial profile. *ITT* Intention to treat

Table 1 Baseline characteristics

Baseline characteristics	**Open-access phase intervention participants ($N = 139$)**
Age (years)	59.3 ± 9.6 [33, 77]
Weight (kg)	97 ± 20 [51, 170]
Body mass index (kg/m^2)	33.1 ± 6.0 [18.8, 54.1]
Duration of diabetes (years)	17 ± 8 [2, 43]
Duration of insulin use (years)	9 ± 6 [0, 40]
Screening HbA1c	
mmol/mol	71.8 ± 10.5 [59, 103]
%	8.72 ± 0.96 [7.5, 11.6]
Self-reported blood glucose frequency per day	3.6 ± 1.29 [1, 10]
Insulin (total daily dose)	
Basal units ($n = 124$)	38.0 ± 21.0
Bolus units ($n = 115$)	51.7 ± 30.4
CSII units ($n = 5$)	56.5 ± 39.5
	Open-access phase intervention participants *N* (%)
Gender (male)	88 (63%)
Ethnicity	
White	134 (96%)
Black	1 (1%)
Asian/Pacific Islander	1 (1%)
Other	3 (2%)
Diabetes management	
Insulin pen device	130 (94%)
CSII	8 (6%)
Insulin syringe	1 (1%)
Previous CGM use	10 (7%)
Employment status	
Employed ($n = 136$)	56 (41%)
Not employed/retired/other ($n = 136$)	80 (59%)
Insulin management training	
<1 year ago	41 (29%)
>1 year ago	93 (67%)

Table 1 continued

	Open-access phase intervention participants*N* (%)
Carbohydrate counting training	
<1 year ago	40 (29%)
>1 year ago	49 (35%)
Bolus dose titration	
Based on meal content ($n = 138$)	89 (64%)
Based on current glucose level ($n = 138$)	108 (78%)
Using sliding scale ($n = 138$)	53 (38%)

Values in table are presented as the mean ± standard deviation (SD) with the range in square brackets or as the number with the percentage in parenthesis, as appropriate

CGM Continuous glucose monitoring, *CSII* continuous subcutaneous insulin infusion, *HbA1c* glycated hemoglobin

from the three (baseline and 6 and 12 months post-baseline) 14-day sensor wear periods.

Significant reductions in all sensor measures of time spent in hypoglycemia [glucose <3.9 mmol/L (70 mg/dL), <3.1 mmol/L (55 mg/dL) and <2.5 mmol/L (45 mg/dL)], number of events and area under the curve were observed for participants at the end of the open-access phase (12 months) compared to the baseline phase (Table 2; Figs. 2, 3).

Time in hypoglycemia [glucose <3.9 mmol/L (70 mg/dL)] was reduced by 50% (−0.70 ± 1.85 h/day; mean ± SD) at 12 months post-baseline compared with baseline ($p = 0.0002$).

Time in hypoglycemia [glucose <3.1 mmol/L (55 mg/dL)] was reduced by 62% (−0.40 ± 1.09 h/day) at 12 months post-baseline compared with baseline ($p = 0.0002$).

Time in hypoglycemia [glucose <2.5 mmol/L (45 mg/dL)] was reduced by 67% (−0.23 ± 0.73 h/day) at 12 months post-baseline compared with baseline ($p = 0.0013$).

Nocturnal hypoglycemia [glucose <3.9 mmol/L (70 mg/dL), 2300–0600 hours] was reduced by 52% (−0.31 ± 0.84 h per 7 h) at 12 months post-baseline compared with baseline ($p = 0.0002$) (Fig. 3).

Daytime hypoglycemia [glucose <3.9 mmol/L (< 70 mg/dL), 0600–2300 hours] was reduced by 48% (−0.38 ± 1.18 h per 17 h) at 12 months post-baseline compared with baseline [$p = 0.0011$ (Fig. 3).

The frequency of events with glucose at <3.9 mmol/L (70 mg/dL) was reduced by 41% (−0.27 ± 0.67, mean ± SD) at 12 months compared with baseline ($p < 0.0001$). The frequency of events with glucose at <3.1 mmol/L (55 mg/dL) was reduced by 56% (−0.20 ± 0.49, $p < 0.0001$), and that of events with glucose at <2.5 mmol/L (45 mg/dL) by 62% (−0.13 ± 0.35) compared with baseline ($p = 0.0002$).

A difference for area under the curve of 58% (−12.73 ± 34.53 h/day × mg/dL, mean ± SD) for sensor glucose level of <3.9 mmol/L (70 mg/dL) was observed at 12 months compared to baseline ($p = 0.0002$). For sensor glucose levels of <3.1 mmol/L (55 mg/dL) and <2.5 mmol/L (45 mg/dL), the area under the curve was reduced by 65% (−4.28 ± 12.76 h/day × mg/dL, $p = 0.0007$) and by 69% (−1.12 ± 3.67 h/day × mg/dL $p = 0.0021$), respectively.

At 12 months post-baseline there was no difference in time in hyperglycemia [>10.0 mmol/L (180 mg/dL), >13.3 mmol/L (240 mg/dL), and >16.7 mmol/L (300 mg/dL)] compared to baseline ($p = 0.1981$, $p = 0.9533$, and $p = 0.8349$, respectively, Fig. 2).

There was also no difference in time in glucose range 3.9–10.0 mmol/L (70–180 mg/dL)] between baseline and 12 months post-baseline

Table 2 Glycemic measures

Measure	Participants (N = 139)					
	Baseline(Days 1–15) (n = 108)Mean (SD)	6-months(Days 194–208) (n = 108)Mean (SD)	Open Access(Days 374–388) (n = 108) Mean (SD)	Open Access % Change from Baseline	Open Access Change fromBaseline Mean (SD)	Open Access Change from Baseline p-value
Time with glucose 3.9–10.0 mmol/L (70–180 mg/dL) (h)	14.0 (4.4)	13.6 (4.5)	14.1 (4.0)	0.6	0.1 (4.4)	0.8519
Mean Glucose (mg/dL)	163.3 (32.7)	175.7 (31.6)	169.9 (27.5)	4.0	6.6 (33.1)	0.0409
Mean Glucose (mmol/L)	9.1 (1.8)	9.8 (1.8)	9.4 (1.5)	4.0	0.4 (1.8)	0.0409
SD Glucose (mg/dL)	55.4 (13.0)	54.7 (13.7)	53.7 (14.3)	−3.1	−1.7 (11.7)	0.1324
SD Glucose (mmol/L)	3.1 (0.7)	3.0 (0.8)	3.0 (0.8)	−3.1	−0.1 (0.7)	0.1324
Glucose <3.9 mmol/L (70 mg/dL) within 24 h						
Events	0.67 (0.66)	0.33 (0.36)	0.40 (0.44)	−40.8	−0.27 (0.67)	<0.0001
Time (h)	1.40 (1.91)	0.47 (0.57)	0.70 (0.94)	−49.9	−0.70 (1.85)	0.0002
AUC (h x mg/dL)	21.84 (37.45)	5.21 (7.28)	9.11 (14.70)	−58.3	−12.73 (34.53)	0.0002
Glucose <3.9 mmol/L (70 mg/dL) at night (23.00–06.00) within 7 h						
Events	0.26 (0.29)	0.13 (0.16)	0.16 (0.22)	−37.8	−0.10 (0.33)	0.0021
Time (h)	0.60 (0.90)	0.20 (0.29)	0.28 (0.42)	−52.3	−0.31 (0.84)	0.0002
AUC (h x mg/dL)	10.29 (19.42)	2.40 (4.34)	4.07 (6.89)	−60.5	−6.22 (17.68)	0.0004
Glucose <3.1 mmol/L (55 mg/dL) within 24 h						
Events	0.36 (0.53)	0.11 (0.17)	0.16 (0.27)	−56.5	−0.20 (0.49)	<0.0001
Time (h)	0.65 (1.20)	0.13 (0.22)	0.25 (0.45)	−62.0	−0.40 (1.09)	0.0002
AUC (h x mg/dL)	6.54 (14.00)	0.95 (1.81)	2.26 (4.67)	−65.4	−4.28 (12.76)	0.0007
Glucose <3.1 mmol/L (55 mg/dL) at night (23.00–06.00) within 7 h						
Events	0.16 (0.23)	0.05 (0.09)	0.07 (0.12)	−55.5	−0.09 (0.21)	<0.0001
Time (h)	0.30 (0.63)	0.06 (0.14)	0.12 (0.22)	−62.1	−0.19 (0.57)	0.0008
AUC (h x mg/dL)	3.30 (7.99)	0.48 (1.26)	1.10 (2.40)	−66.8	−2.21 (7.28)	0.0021
Glucose <2.5 mmol/L (45 mg/dL) within 24 h						
Events	0.21 (0.39)	0.04 (0.07)	0.08 (0.17)	−61.7	−0.13 (0.35)	0.0002
Time (h)	0.34 (0.79)	0.04 (0.08)	0.11 (0.25)	−67.2	−0.23 (0.73)	0.0013
AUC (h x mg/dL)	1.63 (3.96)	0.16 (0.37)	0.51 (1.22)	−68.5	−1.12 (3.67)	0.0021
Glucose <2.5 mmol/L (45 mg/dL) at night (23.00–06.00) within 7 h						
Events	0.09 (0.18)	0.02 (0.07)	0.04 (0.08)	−56.0	−0.05 (0.15)	0.0008
Time (h)	0.17 (0.46)	0.02 (0.07)	0.05 (0.14)	−68.8	−0.12 (0.42)	0.0032
AUC (h x mg/dL)	0.88 (2.45)	0.09 (0.31)	0.25 (0.69)	−71.5	−0.63 (2.26)	0.0045

Table 2 continued

Measure	Participants ($N = 139$)					
	Baseline(Days 1–15) ($n = 108$)Mean (SD)	6-months(Days 194–208) ($n = 108$)Mean (SD)	Open Access(Days 374–388) ($n = 108$) Mean (SD)	Open Access % Change from Baseline	Open Access Change fromBaseline Mean (SD)	Open Access Change from Baseline *p*-value
Time in hyperglycemia						
Time >10.0 mmo/L (180 mg/dL) within 24 h	8.58 (5.84)	9.98 (4.68)	9.20 (4.29)	7.2	0.62 (4.94)	0.1981
Time >13.3 mmo/L (240 mg/dL) within 24 h	2.94 (3.04)	3.54 (3.48)	2.96 (2.81)	0.9	0.03 (3.17)	0.9533
Time >16.7 mmo/L (300 mg/dL) within 24 h	0.72 (1.45)	1.01 (1.93)	0.75 (1.36)	4.3	0.03 (1.53)	0.8349

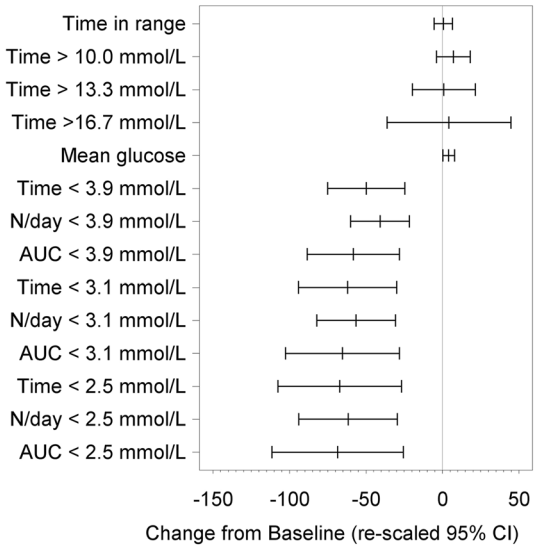

Fig. 2 Difference from baseline for time in range and hypoglycemia measures at 12 months. Rescaled confidence intervals are confidence intervals for the difference from baseline expressed as a percentage of the baseline mean

($p = 0.8519$) or change in glycemic variability [$p = 0.1324$; Table 2 and Fig. 2]. The mean glucose level increased from 9.1 ± 1.8 to 9.4 ± 1.5 mmol/L ($p = 0.0409$).

For the participants who continued into the open-access phase, mean SMBG frequency was 3.9 ± 1.2 (SD) tests/day (median 3.9 tests/day) at baseline, falling to a mean of 0.6 ± 1.2 tests/day (median 0.1) when participants first had full access to sensor glucose data (days 15–31, treatment phase). The mean overall blood glucose monitoring rate for the 6-month treatment phase was 0.3 ± 0.7 tests/day (median 0.1), further reducing to 0.2 ± 0.6 tests/day (median 0.0) during the open-access phase (Fig. 4).

Average sensor-scanning frequency was 7.1 ± 3.5 times/day (median 5.7) during the open-access phase compared to 8.4 ± 4.6 during the 6-month treatment phase (median 6.8 times/day) (Fig. 4). There was no correlation between increased frequency of sensor scanning and reduction in time in hypoglycemia [<3.9 mmol/L (70 mg/dL)] or hyperglycemia [>13.3 mmol/L (240 mg/dL)] between the baseline phase and end of the open-access phase (12 months). Mean device use (defined as the

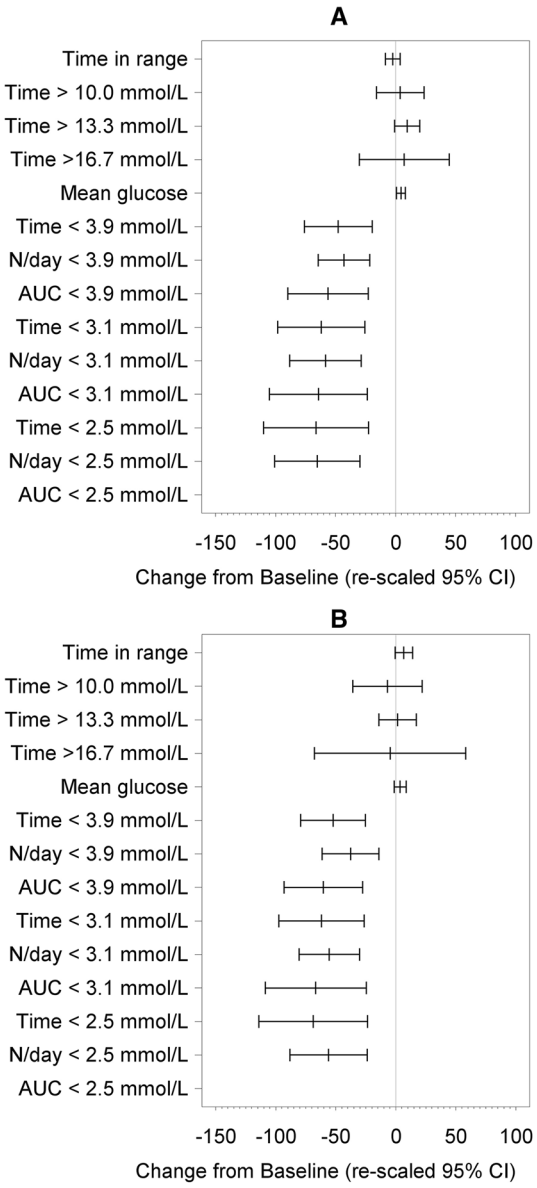

Fig. 3 Summaries of all glycemic measures during the day (0600–2300) (**a**) and during the night (2300–0600) (**b**). Difference from baseline for glycemic measures at 12 months post-baseline. Rescaled confidence intervals are confidence intervals for the difference from baseline expressed as a percentage of the baseline mean

percentage of data collected, assuming continuous device wear) was 83.6% ± 13.8 (median 88.3%) between 6 and 12 months and 88.7 ± 9.2% (median 90.7%) in the treatment phase.

Participants' total daily insulin doses recorded at the penultimate visit (day 284) were

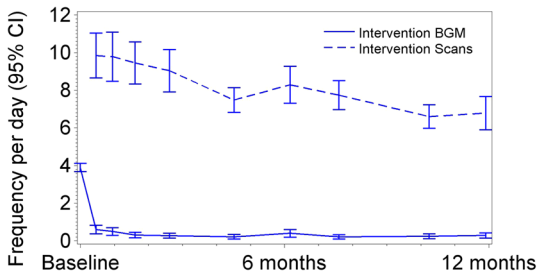

Fig. 4 Blood glucose monitoring tests and sensor scans frequency per day by study period. *BGM* Blood glucose monitoring

unchanged compared to either baseline ($p = 0.4827$) or 6-months post-baseline ($p = 0.7220$).

For those participants aged <65 years ($n = 60$; 56%) and those aged ≥65 years ($n = 48$; 44%), significant reductions in time spent in hypoglycemia [<3.9 mmol/L (70 mg/dL), <3.1 mmol/L (55 mg/dL) and <2.5 mmol/L (45 mg/dL)] were observed at the end of the open-access phase (12 months) compared to the baseline phase (Fig. 5).

Safety

The flash sensor-based system was used for an overall duration of 12 months by participants. During the open-access phase three cardiac events were reported, none of which were related to the study device or study procedure as the three participants had a previous history of cardiovascular disease prior to study entry. There were no reports of diabetic ketoacidosis or hyperosmolar hyperglycemic state.

In total, serious adverse or adverse events ($n = 135$) were experienced by 60 (43%) of 139 participants. There were nine occurrences of a serious adverse event, none of which were related to the device, study procedure, or to hypoglycemia. Nine mild hypoglycemia adverse events were experienced by two participants and were reported by the clinician as not related to the study device at all or to the study procedure. Five participants experienced an adverse event in the open-access phase, leading to withdrawal from the study; two due to death (not associated with the device or study) and

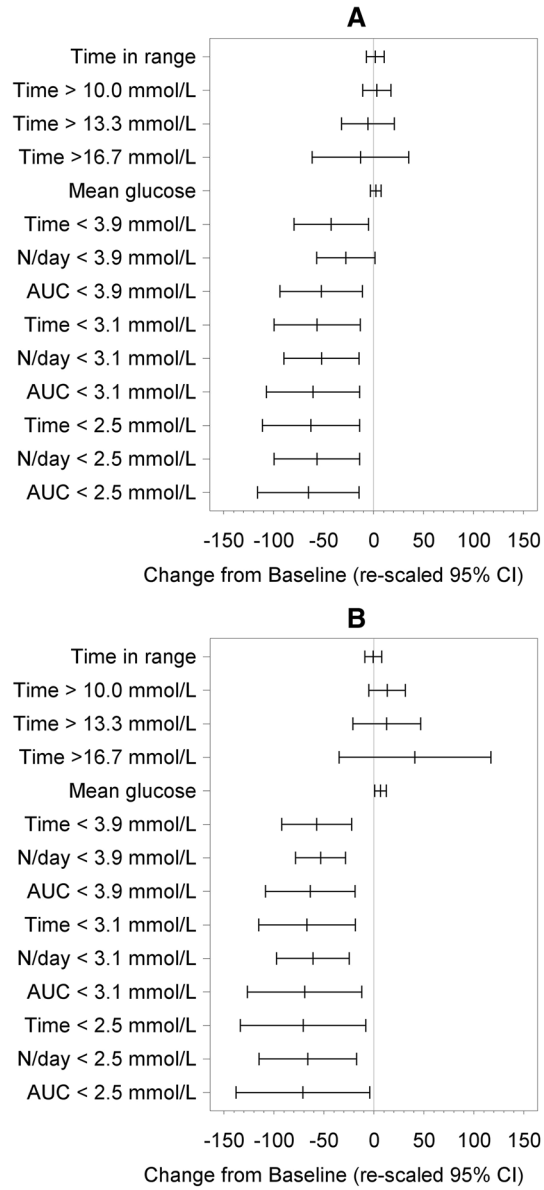

Fig. 5 Summaries of glycemic measures for participants aged <65 years (**a**) and aged ≥65 years (**b**). Difference from baseline for glycemic measures at 12 months. Rescaled confidence intervals are confidence intervals for the difference from baseline expressed as a percentage of the baseline mean

three due to sensor insertion/site reaction. Nine participants reported 16 device-related adverse events; four severe, nine moderate and three mild. These were all sensor-adhesive or site reactions, primarily treated with topical preparations and all were resolved.

Anticipated sensor insertion site symptoms refer to those typically expected using a sensor device and equate to symptoms normally experienced with blood glucose finger-stick testing, such as pain, bleeding, bruising. There were 134 anticipated sensor insertion site symptoms observed for 28 (20%) participants. These symptoms were primarily ($n = 117$; 87%) due to the sensor wear (erythema, itching and rash) and most were resolved without medical intervention; 63 were mild in nature, 67 were moderate and four were severe. Adverse events and anticipated symptoms associated with the insertion of the sensor and sensor wear are summarized in Table 3 and Table S1 in the supplementary material.

DISCUSSION

The REPLACE study was the first to publish data investigating the use of flash sensor-based glucose technology as a replacement for standard SMBG in individuals with type 2 diabetes treated with multi-dose insulin therapy. The findings from the treatment phase of the study have demonstrated that flash glucose monitoring technology is a safe replacement for blood glucose monitoring and that the use of the technology is associated with reduced time in hypoglycemia, particularly nocturnal hypoglycemia [9]. During the additional 6 month open-access phase, reductions in time in hypoglycemia were maintained across all age groups, with sustained benefit continued during nighttime. Our findings from a further 6 months of using flash glucose sensing technology reinforce those from the 6 months of use in the REPLACE study [9], demonstrating that the device is safe with repetitive, consecutive use over an extended period of 12 month for adults, irrespective of age, and that the benefit of reduced hypoglycemia is sustained. In addition, our data reinforce the significant reductions in hypoglycemia shown by Bolinder et al. in the IMPACT study for adults with well-controlled type 1 diabetes using flash technology [11].

The American Diabetes Association (ADA) has resisted defining hypoglycemia numerically as all abnormally low glucose events are

Table 3 Adverse events

Adverse events	Open-access Phase Participants ($N = 139$)
Participants with adverse or serious adverse events	60 (43.2%)
Number of adverse events (excluding serious events)	126
Participants with serious adverse events	7 (5.0%)
Number of serious adverse events	9[a]
Participants with hypoglycemic serious adverse events	0 (0%)
Number of hypoglycemic serious adverse events	0
Participants with hypoglycemic adverse events	2 (1.4%)
Number of hypoglycemic adverse events	9
Participants with device-related adverse events	9 (6.5%)
Number of device-related adverse events	16
Participants discontinuing due to adverse events	5 (3.6%)[b]
Number of adverse events leading to discontinuation	5

Values in table are presented as a number with/without the percentage in parenthesis

[a] This number includes seven serious adverse events reported in the 6-month treatment phase results [9]

[b] In addition, 2 subjects withdrew during the open-access phase due to adverse events experienced during the 6-month treatment phase

potentially harmful [2, 12]. However, both the ADA and the European Association for the Study of Diabetes (EASD) consider glucose levels below 3 mmol/L (54 mg/dL) as serious and clinically important [13] due to the associated risks of cardiac arrhythmias [14, 15] and mortality in type 2 diabetes [16, 17]. Notably, our findings of significantly less time in overall hypoglycemia included time at the lower glucose thresholds, and this benefit was maintained over 12 months. Furthermore, a 30% reduction in hypoglycemia is considered to be clinically significant [2], and the use of flash technology reduced time in hypoglycemia [3.9 mmol/L (70 mg/dL)] by 50% at 12 months compared to baseline.

Time in hypoglycemia began to decrease as soon as participants were able to utilize sensor glucose readings for self-management (day 15 of the treatment phase; Fig. 6) and was significantly reduced at 12 months.

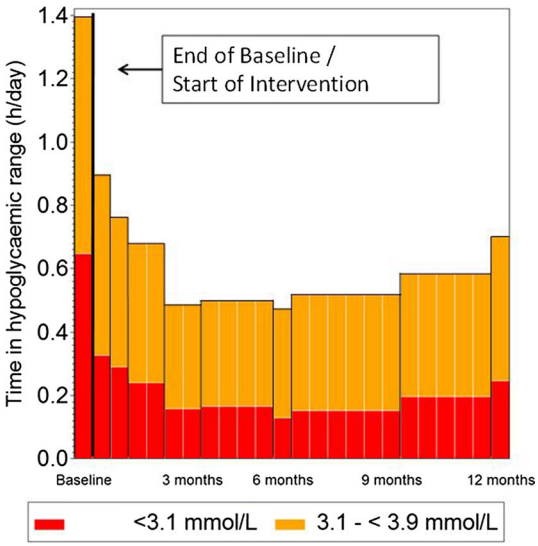

Fig. 6 Significantly reduced time in hypoglycemia is observed as soon as sensor glucose results can be utilized by the participants at the end of the baseline phase and is sustained for 12 months

No change in insulin doses was observed, suggesting that the trend arrow with numerical and graphical sensor glucose information displayed on the reader is of value to support self-management of hypoglycemia detection, prevention and avoidance. The value of continuous monitoring data for self-care modification rather than therapy adjustments has been noted previously for individuals with type 2 diabetes treated with oral therapies [18] and basal insulin [19].

High deployment of the device continued with a utility rate of 84%, and sensor scanning frequency averaged seven times daily with virtually no recourse to blood glucose testing. There was no difference in device use or scanning rate for those younger or older than 65 years, demonstrating confident use of the technology across all adult age groups, which supports current recommendations that those over 65 years should have access to continuous monitoring technology [1].

At the end of the treatment phase, all of the intervention subjects opted to continue into the open-access phase and highly concordant use of the sensor continued. This suggests that flash glucose technology is acceptable as a method of glucose monitoring and that it does not appear to have the same nuisance [20, 21] and variable concordance issues that can be experienced with longer term CGM use [1].

There was no difference in change for time in hyperglycemia compared to baseline at the end of the open-access phase. Of interest, time in hyperglycemia had risen during the treatment phase and subsequently dropped back to baseline values at 12 months. Mean glucose had also risen during the treatment phase and dropped back towards baseline values at 12 months. These apparent rises during the treatment phase were not statistically significantly different to the control group at 6 months. Highly speculative reasoning for this is that previously undetected hypoglycemia, particularly nocturnal, may affect a retrospective fear of hypoglycemia reoccurrence, prompting a resistance to treatment intensification to address hyperglycemia. Although there was no significant change in fear of hypoglycemia in the intervention group compared to the control group [9], any hypoglycemia and especially nocturnal is feared by those with type 2 diabetes [3] and this may partially explain why there was no change in time in hyperglycemia as it was not actively addressed with therapy adjustments.

Similar to the treatment phase, there were no safety concerns during the 12-month-long open-access phase. Skin reactions were reported for nine (6.5%) participants during the open-access phase and six participants (4.0%) in the treatment phase (preceding 6 months). With any medical device that is attached to the body, skin reactions will be experienced by some individuals. Longer duration of sensor wear likely contributes to this [22]. There is little published data on using a device attached to the body with medical grade adhesive; the type of events in our study are similar to those reported for use of flash technology in adults with type 1 diabetes over 6 months [11] and for other systems with on-body sensor use [20, 21].

The original randomized, controlled trial conducted over 6 months included intervention and control participants; only intervention participants continued into the open-access phase for a further 6 months. This is a limitation to our study; however, the primary endpoint of the open-access phase was to assess safety over an extended period of use. A final HbA1c measurement, although of clinical interest, has little value when evaluating safety or the overall effectiveness of flash technology. Similarly, quality of life and patient-reported outcome questionnaires could also have been completed at 12 months. In all phases of the study, our aim was to test the new technology in "real world" conditions. Having restrictive protocols for treatment changes would have made general applicability of our data uncertain. Therefore, this work is limited by the modification of insulin therapy according to local practice rather than using a treatment algorithm. Our inclusion of only adults with type 2 diabetes treated with intensive insulin therapy who performed regular glucose testing means future studies are needed to assess the effectiveness of flash glucose-sensing technology in younger, less concordant, individuals for modifying insulin therapy.

CONCLUSION

In summary, the use of sensor glucose readings over a 12- month period for glucose self-management by individuals with type 2 diabetes treated with intensive insulin therapy was associated with significant and sustained reductions in hypoglycemic measures across all age groups with no safety concerns. Our findings confirm that longer term use of the convenient flash glucose sensing technology is safe and effective and eliminates the need for standard SMBG for glycemic management of type 2 diabetes treated by intensive insulin therapy with multiple daily injections or CSII.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript and take responsibility for the integrity of the work as a whole. Professor Thomas Haak wrote the first draft of the manuscript and together with all the co-authors worked collaboratively to write, discuss and review this manuscript which was revised and edited by Dr. Ramzi Ajjan. All named authors collectively took the decision to submit it for publication and have given final approval to the version to be published.

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Compliance with Ethics Guidelines. Approval was given by the appropriate competent authorities in each country. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL RESEARCH

Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial

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ABSTRACT

Introduction: Glycemic control in participants with insulin-treated diabetes remains challenging. We assessed safety and efficacy of new flash glucose-sensing technology to replace self-monitoring of blood glucose (SMBG).

Methods: This open-label randomized controlled study (ClinicalTrials.gov, NCT02082184) enrolled adults with type 2 diabetes on intensive insulin therapy from 26 European diabetes centers. Following 2 weeks of blinded sensor wear, 2:1 (intervention/control) randomization (centrally, using biased-coin minimization dependant on study center and insulin administration) was to control (SMBG) or intervention (glucose-sensing technology). Participants and investigators were not masked to group allocation. Primary outcome was difference in HbA1c at 6 months in the full analysis set. Prespecified secondary outcomes included time in hypoglycemia, effect of age, and patient satisfaction.

Results: Participants ($n = 224$) were randomized (149 intervention, 75 controls). At 6 months, there was no difference in the change in HbA1c between intervention and controls:

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−3.1 ± 0.75 mmol/mol, [−0.29 ± 0.07% (mean ± SE)] and −3.4 ± 1.04 mmol/mol (−0.31 ± 0.09%) respectively; $p = 0.8222$. A difference was detected in participants aged <65 years [−5.7 ± 0.96 mmol/mol (−0.53 ± 0.09%) and −2.2 ± 1.31 mmol/mol (−0.20 ± 0.12%), respectively; $p = 0.0301$]. Time in hypoglycemia <3.9 mmol/L (70 mg/dL) reduced by 0.47 ± 0.13 h/day [mean ± SE ($p = 0.0006$)], and <3.1 mmol/L (55 mg/dL) reduced by 0.22 ± 0.07 h/day ($p = 0.0014$) for intervention participants compared with controls; reductions of 43% and 53%, respectively. SMBG frequency, similar at baseline, decreased in intervention participants from 3.8 ± 1.4 tests/day (mean ± SD) to 0.3 ± 0.7, remaining unchanged in controls. Treatment satisfaction was higher in intervention compared with controls (DTSQ 13.1 ± 0.50 (mean ± SE) and 9.0 ± 0.72, respectively; $p < 0.0001$). No serious adverse events or severe hypoglycemic events were reported related to sensor data use. Forty-two serious events [16 (10.7%) intervention participants, 12 (16.0%) controls] were not device-related. Six intervention participants reported nine adverse events for sensor-wear reactions (two severe, six moderate, one mild).

Conclusion: Flash glucose-sensing technology use in type 2 diabetes with intensive insulin therapy results in no difference in HbA1c change and reduced hypoglycemia, thus offering a safe, effective replacement for SMBG.

Trial registration: ClinicalTrials.gov identifier: NCT02082184.

Funding: Abbott Diabetes Care.

Keywords: Flash sensor glucose technology; Glucose monitoring; Insulin; Type 2 diabetes

INTRODUCTION

The number of people with diabetes is increasing globally with 90% having type 2 diabetes, a fifth of whom are on insulin treatment. A significant proportion of adults with insulin-treated type 2 diabetes are less than 65 years of age and frequently have poor glycemic control [1, 2]. Improving glycemia reduces the risk of diabetes complications and is a key management objective [3]. However, intensification of insulin therapy increases the risk of hypoglycemia [4] which is associated with adverse clinical outcome [5], impacts on quality of life [6], and increases treatment costs secondary to hospital admissions, ambulance call-outs, and clinic attendance [7]. Glycated hemoglobin (HbA1c), the gold standard for assessment of glycemic control, is unable to reflect hypoglycemic risk or indicate glucose variability, which recent reports suggest are associated with inferior clinical outcome [8, 9]. Detection of hypoglycemia or glucose variability can be difficult with self-monitoring of blood glucose which is usually the main method used for self-management and adjusting insulin therapy. For participants on intensive insulin therapy, four or more blood glucose tests are required daily to safely and effectively adjust insulin doses. This is not always achieved because of the pain and inconvenience associated with this method of glucose testing [10, 11]. A tool that can support a more comprehensive assessment of glycemia is continuous glucose monitoring; however, current devices are costly, require repeated calibration, and are constantly attached to the patient, all key factors preventing widespread use. There is a need for a new method of glucose monitoring that is affordable and provides clear, comprehensive glucose data with minimal patient inconvenience.

We used a novel sensor-based flash glucose monitoring system (FreeStyle Libre™; Abbott Diabetes Care, Witney, UK). The small, single-use, factory-calibrated, on-body sensor utilizes wired enzyme technology (osmium mediator and glucose oxidase enzyme co-immobilized on an electrochemical sensor) to continuously monitor interstitial glucose levels. The sensor is worn on the back of the arm for up to 14 days and automatically stores glucose data every 15 min. A real-time glucose level may be obtained as often as every minute by scanning the sensor with the reader. A glucose trend arrow (indicating rate and direction of change in glucose levels) and a graphical trace of glucose values for the previous 8-h period are also displayed on the screen. Data are transferred by radio frequency identification (RFID) from the sensor to the reader memory which stores historical sensor data for 90 days. This data can be uploaded using the device software to generate summary glucose reports (including an ambulatory glucose profile) for review by the patient at home or in clinic with their healthcare professional (HCP) [12].

The aim of our study was to assess the role of this new category of glucose-sensing technology on glycemic control in individuals with type 2 diabetes using intensive insulin therapy or continuous subcutaneous insulin infusion (CSII).

METHODS

Study Design and Participants

We conducted this 6-month, prospective, open-label, non-masked, two-arm randomized controlled study at 26 European diabetes centers, eight in France, ten in Germany, and eight in the UK (Supplementary Material p. 1).

We enrolled participants aged 18 years or older with type 2 diabetes treated with insulin for at least 6 months and on their current regimen (prandial only or prandial and basal intensive insulin therapy or CSII therapy) for 3 months or more, an HbA1c level 58–108 mmol/mol (7.5–12.0%), self-reported regular blood glucose testing (more than 10/week for at least 2 months prior to study entry), and were considered by the investigator to be technically capable of using the flash sensor-based glucose monitoring system. At each study center, any potentially eligible patient from the general diabetes population was invited to participate in the study.

Participants were not included if they had any other insulin regimen to that described above; a total daily dose of insulin $\geq$1.75 units/kg on study entry; had severe hypoglycemia (requiring third-party assistance) [13], diabetic ketoacidosis, or hyperosmolar-hyperglycemic state in the preceding 6 months; known allergy to medical-grade adhesives; used continuous glucose monitoring within the previous 4 months; were pregnant or planning pregnancy; were receiving steroid therapy for any condition; or were considered by the investigator to be unsuitable to participate.

Approval was given by the appropriate competent authorities in each country. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for participation in the study.

Randomization and Masking

Participants were centrally randomized in a 2:1 ratio to sensor-based flash glucose monitoring

(intervention group) or to self-monitoring of blood glucose (control group) by an interactive web response system (IWRS) using biased-coin minimization, with study center and insulin administration as prognostic factors. The intention of a 2:1 randomization ratio was to ensure a sufficient number of participants in the intervention arm to complete an additional 6-month, open-access study phase. Participants, investigators, and study staff were not masked to group allocation.

Procedures

Following consent, screening, and enrollment, all participants wore a system locked into masked mode for the 14-day baseline period and were asked to scan their sensor every 8 h. Sensor glucose measurements were blinded (not visible) to participants and investigators during this phase. Glucose management was supported by continuation of their current regimen for blood glucose monitoring using the strip-port built into the reader and compatible test strips (Abbott Diabetes Care, Witney, Oxon, UK). Participants were asked to record blood glucose levels in a glucose diary and to log other events (e.g., severe hypoglycemia) in an event diary. Participants with sensor data for at least 50% of the blinded wear or at least 650 individual sensor readings (only two subjects did not meet this criterion and withdrew) were centrally randomized to intervention or control group.

For the 6-month treatment phase (post-randomization), the sensor-based glucose monitoring system was unblinded for intervention participants to continuously use sensor glucose data for self-management, including insulin dose decisions, in accordance with the product labelling. No training was provided to these participants for interpretation of glucose sensor data. Their historical data was uploaded at subsequent study visits and glucose reports were generated for review by the HCP with the participant, using the device software [12].

Control participants self-managed their glucose levels utilizing a standard blood glucose device (Abbott Diabetes Care, Witney, UK) and a glucose diary for the duration of the study, wearing a blinded sensor again for the last 2 weeks of the study.

Between randomization and day 194, intervention and control participants had two visits. At these visits, participants' glucose control was reviewed with an HCP and the effects of diet/lifestyle on glucose trends and insulin dose modifications were discussed. There was no preset algorithm for insulin adjustments mandated by the protocol in order to reflect "real-world". However, common principles were applied that included avoidance of hypoglycemia, optimization of fasting glucose levels, and reduction of postprandial glucose excursions. Intervention participants had a safety visit (day 45) as the device was not on-market when the study commenced.

HbA1c was measured in all participants at baseline, 3 and 6 months with analysis by a central laboratory (ICON Laboratories, Dublin, Ireland).

All participants completed quality of life and patient-reported outcome questionnaires [14–16] prior to other study activities on day 1 and on day 194.

Outcomes

The primary outcome was the difference in HbA1c between intervention and control groups at 6 months. Prespecified secondary endpoints were subgroup analyses by age (less

than and 65 years or older), sensor-derived glycemic measures from baseline to days 194–208, frequency of glucose finger-sticks and sensor scans per day during the study period, system utilization for days 15–208 (defined as the percentage of data collected, assuming continuous device wear), and change in total daily dose of insulin, body mass index (BMI), weight, and participant questionnaire responses. Sensor-derived glycemic measures comprised number and duration of hypoglycemic events (<3.9 mmol/L [70 mg/dL], and <3.1 mmol/L [55 mg/dL]); time in range (3.9–10.0 mmol/L [70–180 mg/dL]), number and duration of hyperglycemic events (>10.0 mmol/L [180 mg/dL], and >13.3 mmol/L [240 mg/dL]), mean glucose, and glucose variability measures [17–19]). An event was defined as at least two consecutive readings, at 15-min intervals, outside the predefined glucose range (the end of an episode was one reading at or inside the predefined range).

Secondary endpoints reported in the clinical study report and not here, include change in HbA1c from baseline to day 105, proportion of participants with reduction in HbA1c of ≥5.5 mmol/mol (0.5%) from baseline, or achieving HbA1c ≤ 58 mmol/mol (7.5%), post-prandial hyperglycemia, blood pressure, lipid levels, HCP questionnaire responses, emergency room visits, hospital admissions, additional clinic time, lancet use and non-insulin medication use.

Results for the user questionnaire (intervention participants only) were assessed at 6 months. Patient-reported outcome and quality of life (QoL) measures were assessed using validated questionnaires: Diabetes Distress Scale (DDS) [14], Diabetes Quality of Life (DQoL) [15], and Diabetes Treatment Satisfaction (DTSQs and DTSQc) [16].

Safety endpoints incorporated all adverse events including severe hypoglycemia (requiring third-party assistance) [13], hypoglycemic events [20], sensor insertion or sensor wear-related symptoms, diabetic ketoacidosis or hyperosmolar hyperglycemic state episodes, and cardiac events.

Statistical Analysis

This study was powered at 90% to detect a difference of 3.8 mmol/mol (0.35%) in HbA1c between the intervention and control group at 6 months with a 5% significance level as per guidance of the Food and Drug Administration [21] and assuming SD for the change of 0.65 [22]. The intervention group was double the size of the control group resulting in a sample size of 210 participants allowing for a dropout rate of 20% post-randomization. Missing values for the primary endpoint were imputed using the last observation carried forward (LOCF) approach. For the sensor data derived secondary endpoints, if less than 72 h of sensor results were available from the final 14-day sensor wear (days 194–208), the last 72 h of available recorded results were used. Analysis of covariance was used to adjust for chance imbalances in baseline measurements between the treatment groups [23], adjusted means were then used to compare differences between the groups for the 6-month endpoints.

Glycemic control and variability results, BMI/weight, and total daily dose of insulin were compared between treatment groups using analysis of covariance of the differences between post-baseline and baseline values with study center and baseline measurement as covariates.

Changes in questionnaire responses were considered using analysis of covariance on

baseline values and study center to compare scores from intervention with control group participants.

Confidence intervals were calculated for the group least-square mean of each measure and the difference between group least-square means.

Results presented here are for the full analysis set, which included all randomized participants since there were no pregnancies.

Data analysis was performed by a contract research organization (ICON PLC; Dublin, Ireland, managed by Abbott Diabetes Care) and by Abbott Diabetes Care. We used SAS version 9.2 or higher for all analyses.

The trial is registered with ClinicalTrials.gov (NCT02082184).

Role of the Funding Source

The sponsor designed the study protocol in collaboration with the principal investigator in each country and provided all study materials. The sponsor was involved in collecting data and reporting results, but was not involved in the authors' interpretation or text writing. The sponsor also gave approval to submit for publication. The corresponding author had full access to all the data in the study and, together with all authors, had final responsibility for the decision to submit for publication.

RESULTS

We recruited 302 participants between March 13 and October 15, 2014; 224 were randomized (149 intervention, 75 controls) after completing the baseline phase (Fig. 1). Prior to randomization 78 participants discontinued, the primary reason for this was failure to meet screening HbA1c criterion. Participants' baseline characteristics are summarized in Table 1, the full analysis set included 224 randomized participants, and there were no significant differences between groups.

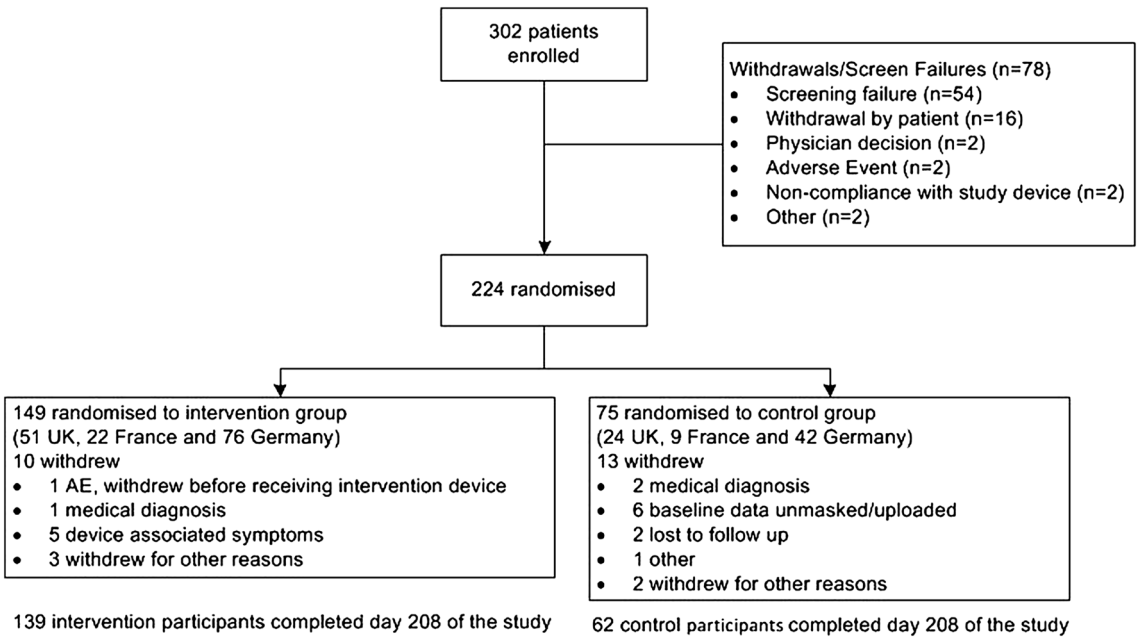

Fig. 1 Trial profile

Table 1 Baseline characteristics

	Intervention ($N = 149$)	**Control ($N = 75$)**
Age (years)	59.0 ± 9.9 (33, 81)	59.5 ± 11.0 (22, 80)
Weight (kg)	98 ± 21 (51, 170)	99 ± 19 (61, 161)
BMI (kg/m^2)	33.1 ± 6.2 (18.8, 54.1)	33.3 ± 5.5 (23.7, 52.4)
Duration of diabetes (years)	17 ± 8 (2, 43)	18 ± 8 (4, 37)
Duration of insulin use (years)	9 ± 6 (0, 40)	10 ± 7 (1, 35)
Screening HbA1c (mmol/mol)	72.0 ± 10.6 (59, 103)	73.5 ± 11.3 (59, 104)
(%)	8.74 ± 0.97 (7.5, 11.6)	8.88 ± 1.04 (7.5, 11.7)
Self-reported blood glucose frequency per day	3.6 ± 1.28 (1, 10)	3.9 ± 1.33 (2, 10)
Insulin, total daily dose		
Basal (units)	40.4 ± 22.6 ($n = 138$)	42.3 ± 25.1 ($n = 70$)
Bolus (units)	50.5 ± 32.5 ($n = 141$)	54.8 ± 32.7 ($n = 70$)
CSII (units)	76.9 ± 49.8 ($n = 8$)	82.6 ± 37.0 ($n = 3$)
Gender, male	94 (63%)	56 (75%)
White	141 (95%)	70 (93%)
Black	2 (1%)	1 (1%)
Asian/Pacific Islander	3 (2%)	2 (3%)
Other	3 (2%)	2 (3%)
Insulin pen device	140 (94%)	71 (95%)
CSII	8 (5%)	4 (5%)
Insulin syringe	1 (1%)	0 (0%)
Previous CGM use	11 (7%)	4 (5%)
Employed	62 (42%)	34 (45%)
Not employed/retired/other	83 (56%)	40 (53%)
Insulin management training		
<1 year ago	44 (30%)	28 (37%)
>1 year ago	100 (67%)	42 (56%)
Carbohydrate counting training		
<1 year ago	44 (30%)	27 (36%)
>1 year ago	53 (36%)	25 (33%)
Bolus dose titration based on meal content	96 (64%)	47 (63%)
Bolus dose titration based on current glucose level	116 (78%)	60 (80%)
Bolus dose titration using sliding scale	57 (38%)	32 (43%)

Data are presented as mean ± SD (min, max) or *n* (%)

There was no difference in HbA1c change at 6 months between intervention and control groups [−3.1 ± 0.75 mmol/mol (adjusted mean ± SE), (−0.29 ± 0.07%) and −3.4 ± 1.04, (−0.31 ± 0.09%), respectively; $p = 0.8222$]. A similar drop in HbA1c was detected in both groups comparing study end to baseline values.

In participants younger than 65 years, a prespecified subgroup, the drop in HbA1c was more pronounced in the intervention group compared with controls [−5.7 ± 0.96 mmol/mol, (adjusted mean ± SE) (−0.53 ± 0.09%) and −2.2 ± 1.31 mmol/mol (−0.20 ± 0.12%), respectively; $p = 0.0301$ (Supplementary Material p. 2)]. A significant interaction between treatment group and age was observed for change in HbA1c ($p = 0.0017$).

In participants aged 65 years or more, the drop in HbA1c was more pronounced for the controls compared to the intervention group [−5.4 ± 1.45 mmol/mol (−0.49 ± 0.13%)] and [−0.6 ± 1.09 mmol/mol (−0.05 ± 0.10%), respectively, $p = 0.0081$ (Supplementary Material p. 3)].

Significant reductions in all sensor measures of time spent in hypoglycemia, number of events, and area under the curve were observed for intervention participants compared with control (Table 2, Fig. 2, and Supplementary Material pp. 4–7).

Time in hypoglycemia [<3.9 mmol/L (70 mg/dL)] reduced by 43% (−0.47 ± 0.13 h/day; mean ± SE) for intervention participants compared with control ($p = 0.0006$).

Time in hypoglycemia [<3.1 mmol/L (55 mg/dL)] reduced by 53% (−0.22 ± 0.068 h/day) for intervention participants compared with control ($p = 0.0014$).

Time in hypoglycemia [<2.5 mmol/L (45 mg/dL)] reduced by 64% (−0.14 ± 0.04 h/day) for intervention participants compared with control ($p = 0.0013$).

Nocturnal hypoglycemia [<3.9 mmol/L (70mg/dL), 23.00–06.00 h] reduced by 54% (−0.29 ± 0.08 h per 7 h) for intervention participants compared with control ($p = 0.0001$).

Daytime hypoglycemia [<3.9 mmol/L (<70 mg/dL), 06.00–23.00 h] reduced by 31% (−0.16 ± 0.08 h per 17 h) for intervention participants compared with control ($p = 0.0374$).

The frequency of events with glucose <3.9 mmol/L (70 mg/dL) reduced by 28% (−0.16 ± 0.065 per day mean ± SE) for intervention participants compared with controls ($p = 0.0164$). Events <3.1 mmol/L (55 mg/dL) reduced by 44% (−0.12 ± 0.037) for intervention participants compared with controls ($p = 0.0017$). Frequency of events <2.5 mmol/L (45 mg/dL) reduced by 49% (−0.06 ± 0.02) for intervention participants compared with controls ($p = 0.0098$).

A between-group difference for area under the curve of 51% (−7.80 ± 2.20 h/day × mg/dL mean ± SE) for sensor glucose level <3.9 mmol/L (70 mg/dL) was observed for intervention versus control participants ($p = 0.0005$). For sensor glucose levels <3.1 mmol/L (55 mg/dL), area under the curve reduced by 60% (−2.51 ± 0.76 h/day × mg/dL) for intervention participants compared with controls ($p = 0.0012$). Area under the curve was also significantly reduced by 67% (−0.70 ± 0.22 h/day × mg/dL) at glucose levels <2.5 mmol/L (45 mg/dL) for intervention compared with control participants ($p = 0.0015$).

For the prespecified subgroup aged less than 65 years, time in hypoglycemia [<3.9 mmol/L (70 mg/dL)] reduced by 35% for intervention participants compared to control (−0.37 ± 0.168 h/day, $p = 0.0279$) with 40% reduction in area under the curve ($p = 0.0305$)

Table 2 Glycemic and glucose variability measures

Glycemic measure	Baseline mean (SD)		Study end mean (SD)		Difference in adjusted means in intervention vs control (SE)	Difference in intervention vs control (%)	*p* value
	Intervention (*n* = 149)	Control (*n* = 75)	Intervention (*n* = 149)	Control (*n* = 75)			
HbA1c (mmol/mol)	71.0 (11.1)	72.1 (10.7)	68.0 (9.0)	67.7 (12.4)	0.3 (1.25)	N/A	0.8259
HbA1c (%)	8.65 (1.01)	8.75 (0.98)	8.37 (0.83)	8.34 (1.14)	0.03 (0.114)	N/A	0.8222
Time with glucose 3.9–10.0 mmol/L (70–180 mg/dL) (h)	13.9 (4.5)	13.5 (5.2)	13.6 (4.6)	13.2 (4.9)	0.2 (0.58)	1.1	0.7925
Glucose <3.9 mmol/L (70 mg/dL) within 24 h							
Events	0.64 (0.63)	0.63 (0.66)	0.38 (0.45)	0.53 (0.59)	−0.16 (0.065)	−27.7	0.0164
Time (h)	1.30 (1.78)	1.08 (1.58)	0.59 (0.82)	0.99 (1.29)	−0.47 (0.134)	−43.1	0.0006
AUC (h × mg/dL)	20.15 (35.21)	14.05 (26.35)	7.23 (12.35)	13.59 (22.31)	−7.80 (2.20)	−51.1	0.0005
Glucose <3.9 mmol/L (70 mg/dL) at night (23.00–06.00) within 7 h							
Events	0.25 (0.28)	0.27 (0.32)	0.14 (0.20)	0.27 (0.33)	−0.12 (0.03)	−44.9	0.0003
Time (h)	0.55 (0.84)	0.49 (0.71)	0.23 (0.43)	0.51 (0.72)	−0.29 (0.08)	−54.3	0.0001
Glucose <3.1 mmol/L (55 mg/dL) within 24 h							
Events	0.34 (0.50)	0.27 (0.44)	0.14 (0.24)	0.24 (0.36)	−0.12 (0.037)	−44.3	0.0017
Time (h)	0.59 (1.13)	0.38 (0.83)	0.19 (0.37)	0.37 (0.69)	−0.22 (0.068)	−53.1	0.0014
AUC (h × mg/dL)	6.02 (13.23)	3.40 (9.16)	1.64 (3.85)	3.66 (7.97)	−2.51 (0.76)	−60.3	0.0012
Glucose <3.1 mmol/L (55 mg/dL) at night (23.00–06.00) within 7 h							
Events	0.15 (0.23)	0.13 (0.20)	0.06 (0.13)	0.13 (0.21)	−0.07 (0.02)	−53.0	0.0012
Time (h)	0.27 (0.58)	0.18 (0.35)	0.09 (0.22)	0.19 (0.40)	−0.12 (0.04)	−58.1	0.0032
Glucose <2.5 mmol/L (45 mg/dL) within 24 h							
Events	0.19 (0.37)	0.13 (0.34)	0.06 (0.13)	0.11 (0.25)	−0.06 (0.02)	−48.8	0.0098
Time (h)	0.32 (0.74)	0.17 (0.54)	0.08 (0.21)	0.19 (0.45)	−0.14 (0.04)	−64.1	0.0013
AUC (h × mg/dL)	1.52 (3.77)	0.77 (2.63)	0.35 (1.11)	0.93 (2.23)	−0.70 (0.22)	−66.7	0.0015

Table 2 continued

Glycemic measure	Baseline mean (SD)		Study end mean (SD)		Difference in adjusted means in intervention vs control (SE)	Difference in intervention vs control (%)	*p* value
	Intervention (*n* = 149)	Control (*n* = 75)	Intervention (*n* = 149)	Control (*n* = 75)			
Glucose <2.5 mmol/L (45 mg/dL) at night (23.00–06.00) within 7 h							
Events	0.08 (0.17)	0.06 (0.14)	0.03 (0.08)	0.07 (0.16)	−0.04 (0.02)	−57.8	0.0086
Time (h)	0.16 (0.42)	0.08 (0.23)	0.04 (0.12)	0.11 (0.28)	−0.08 (0.03)	−68.3	0.0041
Glucose <2.2 mmol/L (40 mg/dL) within 24 h							
Events	0.13 (0.30)	0.10 (0.30)	0.05 (0.13)	0.09 (0.22)	−0.05 (0.02)	−52.6	0.0199
Time (h)	0.22 (0.57)	0.12 (0.43)	0.05 (0.17)	0.14 (0.34)	−0.10 (0.03)	−66.7	0.0020
Time with glucose >10.0 mmol/L (180 mg/dL) (h)	8.8 (5.0)	9.4 (5.8)	9.8 (4.8)	9.8 (5.4)	0.3 (0.63)	3.5	0.5970
Time with glucose >13.3 mmol/L (240 mg/dL) (h)	3.1 (3.3)	3.9 (4.5)	3.5 (3.7)	3.9 (4.2)	0.1 (0.46)	2.1	0.8729
Glucose variability							
BGRI	9.5 (5.1)	10.4 (6.7)	9.9 (5.6)	10.5 (6.1)	0.0 (0.70)	N/A	0.9431
CV glucose (%)	34.1 (7.2)	33.1 (6.7)	31.4 (6.2)	33.0 (8.0)	−2.26 (0.71)	N/A	0.0017
LBGI	1.1 (1.3)	1.0 (1.2)	0.6 (0.7)	0.9 (1.0)	−0.3 (0.11)	N/A	0.0029
MAGE (mg/dL; average)	128 (29)	131 (33)	125 (29)	131 (33)	−4 (3.3)	N/A	0.1909
Mean glucose (mg/dL)	165 (34)	171 (43)	174 (33)	174 (38)	3 (4.3)	N/A	0.4236
Standard deviation of glucose (mg/dL)	56 (14)	56 (15)	54 (13)	56 (15)	−1.67 (1.45)	N/A	0.2538
CONGA 2 h (mg/dL)	49 (11)	50 (14)	47 (12)	51 (11)	−3 (1.3)	N/A	0.0385
CONGA 4 h (mg/dL)	61 (16)	61 (19)	57 (18)	64 (17)	−5 (2.2)	N/A	0.0133
CONGA 6 h (mg/dL)	63 (21)	62 (22)	58 (23)	65 (23)	−8 (3.0)	N/A	0.0046

AUC area under curve, *BGRI* blood glucose risk index, *CV* coefficient of variation, *LBGI* low blood glucose index, *MAGE* mean amplitude of glycemic excursions, *CONGA* continuous overall net glycemic action × hours

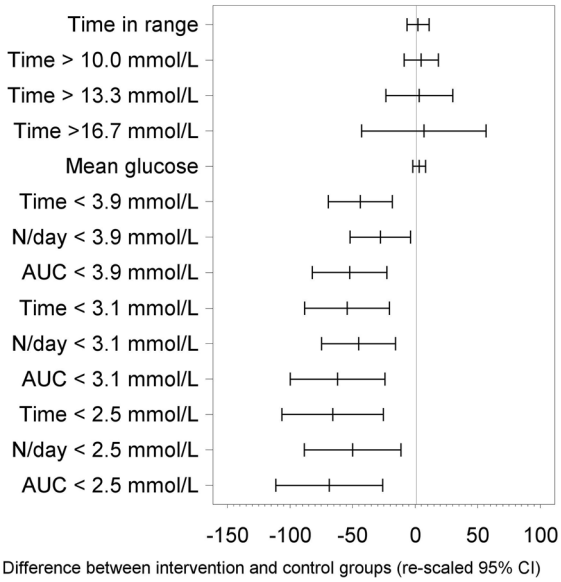

Fig. 2 Difference in intervention and control groups for time in range and hypoglycemia measures. Rescaled confidence intervals are confidence intervals for the difference in the intervention and control group at 6 months expressed as a percentage of the control group adjusted mean

and no difference in the number of events. A trend towards reduced time and events for hypoglycemia at other thresholds was observed (Supplementary Material p. 2).

For participants 65 years or more, time in hypoglycemia (<3.9 mmol/L [70 mg/dL]) reduced by 56% for intervention participants compared to control (-0.60 ± 0.220, $p = 0.0083$) with 71% reduction in area under the curve ($p = 0.0061$). No difference was detected in number of events ($p = 0.0513$). Reduced time, events, and area under the curve for hypoglycemia at other thresholds was observed (Supplementary Material p. 3).

There was no difference in time in range (3.9–10.0 mmol/L (70–180 mg/dL)] between intervention and control participants [$p = 0.7925$, (Table 2)].

There was no difference in time in hyperglycemia [>10.0 mmol/L (180 mg/dL) and >13.3 mmol/L (240 mg/dL)] between the two groups (Table 2).

A number of glucose variability measures were explored and an improvement for intervention participants was observed (Table 2 and Supplementary Material pp. 8–9).

Glucose variability measured as coefficient of variation (CV) reduced by $2.26 \pm 0.71\%$ mean ± SE for intervention participants compared with controls ($p = 0.0017$). LBGI reduced by 0.3 ± 0.11 mean ± SE for intervention participants compared with controls ($p = 0.0029$). CONGA was reduced for intervention compared with controls by 3 ± 1.3 mg/dL mean ± SE at 2 h time interval ($p = 0.0385$), by 5 ± 2.2 at 4 h ($p = 0.0133$), and by 8 ± 3.0 at 6 h ($p = 0.0046$).

Self-monitoring blood glucose frequency for intervention participants fell from 3.8 ± 1.4 tests/day mean ± SD (3.8 tests/day median) at baseline to 0.5 ± 1.1 (0.1 median) from the first unblinded sensor wear with full access to sensor glucose data (day 15–31), reducing further to 0.4 ± 1.0 tests/day (0.0 median) by study end (day 208). The overall blood glucose monitoring rate over 6 months was 0.3 ± 0.7, median 0.1 (Fig. 3).

During the treatment phase (day 15 onwards) average sensor-scanning frequency was 8.3 ± 4.4 (mean ± SD) times/day (median 6.8), i.e., double the frequency of blood glucose testing (Fig. 3). There was no significant difference in the number of scans performed by those <65 years and ≥65 years of age [8.1 ± 4.6 (median 6.8) and 8.5 ± 4.1 (median 6.9), respectively, $p = 0.6627$].

There was no correlation between frequency of sensor scanning and reduced time in hypoglycemia or change to HbA1c. Device use for the intervention group ($n = 138$) was $88.7 \pm 9.2\%$ (defined as the percentage of data

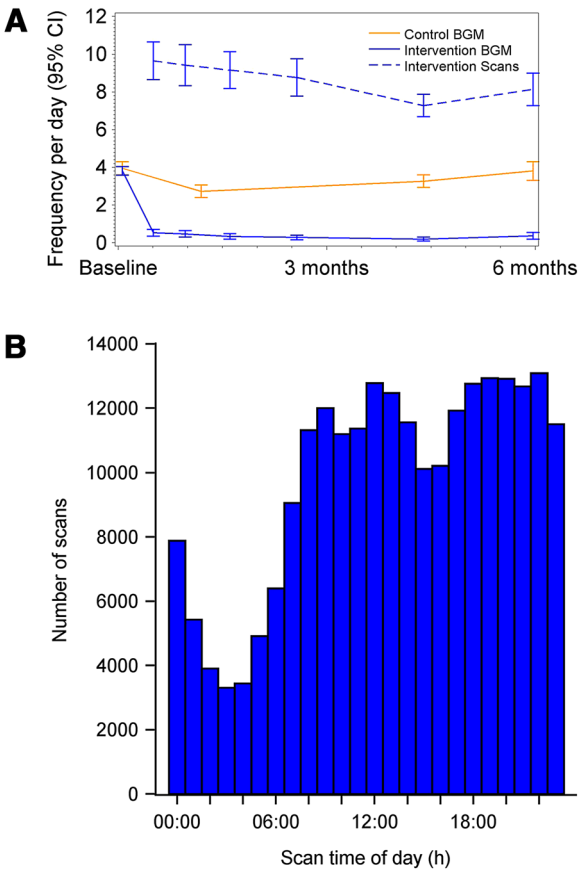

Fig. 3 Glucose monitoring frequency (**a**) and total number of scans by time of day in the intervention group (**b**). Number of scans performed across all intervention participants over 6 months by time of day. *BGM* blood glucose monitoring

collected, assuming continuous device wear for 6 months).

Self-monitoring of blood glucose frequency for control participants was 3.9 ± 1.5 test/day (median 3.9) at baseline and this rate was maintained until study end [3.8 ± 1.9 (median 3.9), Fig. 3]. Control group participants <65 years performed less blood glucose monitoring tests (2.78 ± 1.08 test/day) than those ≥65 years (3.46 ± 0.94), $p = 0.0247$.

At baseline, 95% of participants used an insulin pen device or syringe for intensive insulin therapy, with the remainder (5%) on CSII (Table 1); 78% used analogue insulin, seven participants from each group ($n = 14$) utilized human insulin, and 35 participants used both human and analogue insulin (intervention $n = 22$, control $n = 13$).

There was no difference detected in total daily dose of insulin, basal, or bolus insulin doses between the two groups. None of the changes in insulin were correlated with the treatment effect on HbA1c or time in hypoglycemia (<3.9 mmol/L [70 mg/dL]).

There was no difference in total daily dose of insulin by study end for intervention participants (from 87.6 ± 44.0 (mean ± SD) to 85.2 ± 39.7 units) compared with controls (from 90.1 ± 40.6 to 87.8 ± 41.5), −0.4 ± 3.75 units mean ± SE ($p = 0.9059$). Basal insulin was similar for intervention and control participants (−2.3 ± 1.96 units mean ± SE, $p = 0.2498$). Bolus insulin was similar for intervention and control participants (1.4 ± 2.53 units mean ± SE, $p = 0.5856$). Similarly, for participants above or below 65 years, there was no difference detected in the total daily dose of insulin (0.7 ± 4.86, $p = 0.8871$; and −3.3 ± 5.40, $p = 0.5403$, respectively).

There were no changes in body weight ($p = 0.2496$) or BMI ($p = 0.2668$) from baseline for either group.

Total treatment satisfaction score for DTSQ (status versus change) was significantly improved for intervention group participants (13.1 ± 0.50, mean ± SE) compared with controls (9.0 ± 0.72), $p < 0.0001$. Satisfaction with treatment results using DQoL demonstrated significant improvement for the intervention group (−0.2 ± 0.04, mean ± SE) versus the control group (0.0 ± 0.06), $p = 0.0259$, for this element of the questionnaire. There were no other significant differences observed in other aspects of DTSQ

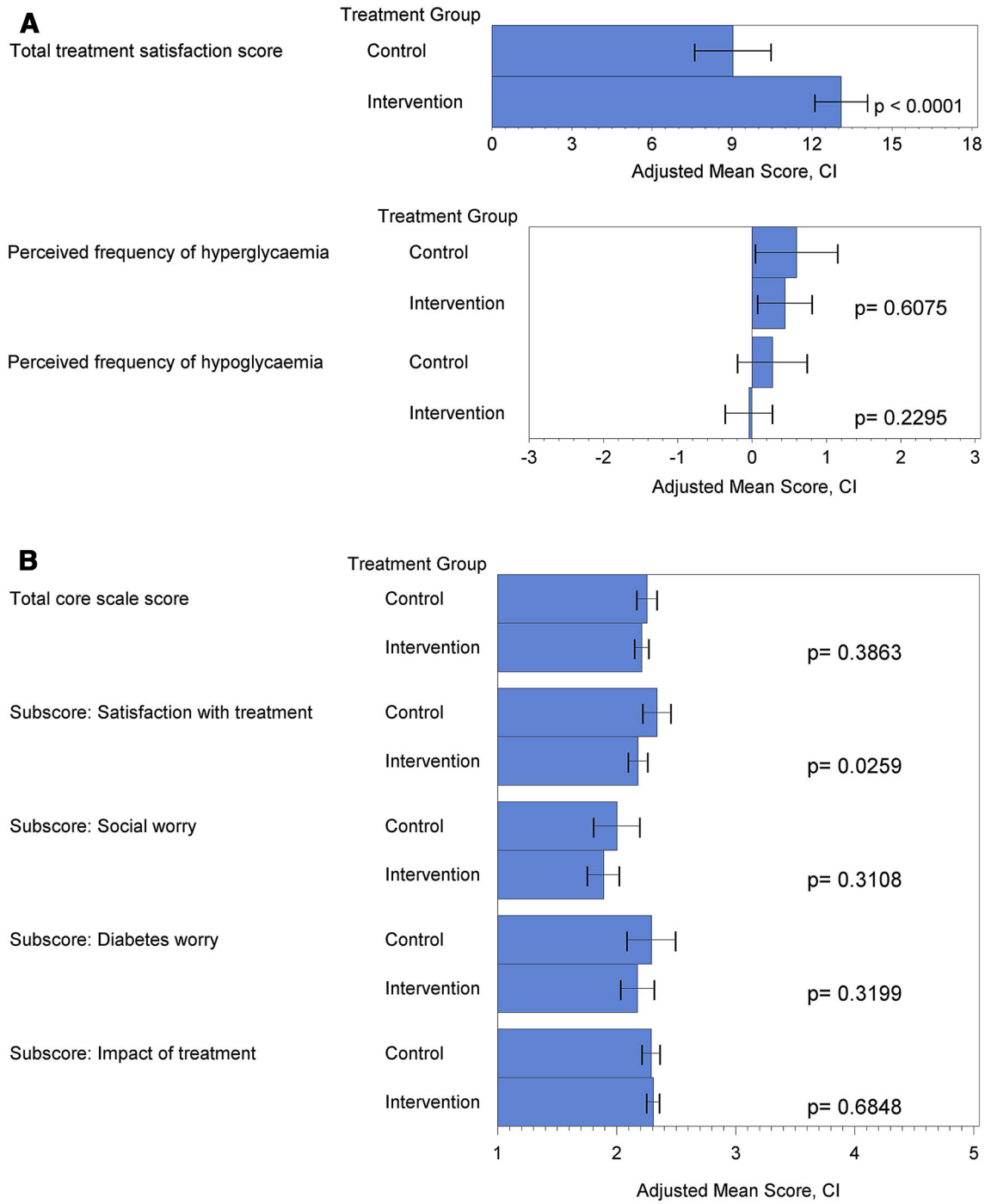

Fig. 4 Scores from DTSQ (**a**) and DQoL (**b**) questionnaires. *Error bars* show 95% CIs. DTSQ treatment satisfaction scores range from −18 to 18; high scores indicate much more satisfied, convenient, flexible, or likely to recommend treatment now. DTSQ perceived frequency scores range from −3 to 3; high scores indicate much more time now. DQoL scores range from 1 to 5; high scores indicate dissatisfaction, frequent impact, or frequent worry. *DQoL* Diabetes Quality of Life Questionnaire, *DTSQ* Diabetes Treatment Satisfaction Questionnaire

and DQoL or for the DDS scales (Fig. 4, Supplementary Material p. 10).

User questionnaire results showed intervention participants agreed with positive aspects of the device including use, comfort, and utilization of sensor glucose information (Supplementary Material p. 11).

The system was used for 6 months by intervention participants and worn (blinded) for 4 weeks by control participants ($n = 224$). In total, serious adverse or adverse events ($n = 515$) were experienced by 114 (76.5%) intervention and 47 (62.7%) control participants.

There were no serious adverse events related to the device or study procedure. Forty-two serious events were experienced by 16 (10.7%) intervention and 12 (16.0%) control participants.

Four hypoglycemia serious adverse events were experienced by four participants (three intervention and one control) and 57 hypoglycemia adverse events by 10 (7%) intervention and seven (9%) control participants.

None of the severe hypoglycemic episodes [13] or hypoglycemic adverse events were associated with the device.

Three participants (one intervention, two controls) experienced an adverse event leading to withdrawal from the study; none were associated with the device.

Six (4.0%) intervention participants reported nine device-related adverse events (two severe, six moderate, and one mild). These were sensor-adhesive reactions, primarily treated with topical preparations. All were resolved at study exit.

There were no reported events of diabetic ketoacidosis or hyperosmolar hyperglycemic state. Seven cardiac events were reported for four (2.7%) intervention and three (4.0%) control participants (none were considered to be related to study procedures or the device).

Anticipated symptoms refer to those typically expected using a sensor device and equate to symptoms normally experienced with blood glucose finger-stick testing, e.g., pain, bleeding, bruising. There were 158 anticipated sensor insertion site symptoms observed for 41 (27.5%) intervention and 9 (12.0%) control participants. These symptoms were primarily (63%) due to the sensor adhesive (erythema, itching, and rash) and resolved without medical intervention. Adverse events and anticipated symptoms associated with the insertion of the sensor and sensor wear are summarized in Table 3 and Supplementary Material p. 12.

DISCUSSION

This European study is the first to investigate the use of flash sensor-based glucose technology as a replacement for standard self-monitoring of blood glucose in individuals with type 2 diabetes treated with intensive insulin therapy. Whilst the primary endpoint was not achieved (no difference in HbA1c change between the groups at 6 months), the secondary endpoints demonstrate a number of interesting findings for further consideration including use of the technology is associated with reduced time in hypoglycemia, particularly nocturnal; treatment satisfaction improved across two questionnaire methodologies; HbA1c improvement combined with reduced hypoglycemia measures were observed in the <65 years subgroup; and the safety data confirms that flash glucose monitoring technology is an effective and safe replacement for blood glucose monitoring.

There is a paucity of data on continuous glucose monitoring (CGM) use in type 2

Table 3 Adverse events

	Intervention ($N = 149$)	Control ($N = 75$)
Participants (%) with adverse or serious adverse events	114 (77%)	47 (63%)
Number of adverse events (excluding serious events)	316	157
Participants (%) with serious adverse events	16 (11%)	12 (16%)
Number of serious adverse events	20	22
Participants with hypoglycemic serious adverse events	3 (2%)	1 (1%)
Number of hypoglycemic serious adverse events	3	1
Participants (%) with hypoglycemic adverse events	10 (7%)	7 (9%)
Number of hypoglycemic adverse events	27	30
Participants (%) with device-related adverse events	6 (4%)	0
Number of device-related adverse events	9*	0
Number of adverse events leading to discontinuation	1	3
Participants (%) discontinuing due to adverse events	1 (1%)	2 (3%)

* All sensor adhesive reactions; 2 severe, 6 moderate, and 1 mild

diabetes and, to our knowledge, no recent randomised, controlled studies in this population using intensive insulin therapy. Available data for CGM use in those using oral glucose-lowering medication or basal insulin with higher baseline HbA1c values indicate they are more likely to show benefit with a reduction in this clinical marker [24–26]. However, hypoglycaemia was not an endpoint in these studies, and exposure to hypoglycaemic risk is much less in treatment regimens excluding prandial insulin. Reductions in hypoglycaemic markers generally require de-escalation of glucose-lowering therapy [27] with less stringent glucose targets [28]. In the intervention group, HbA1c level improved with significantly reduced exposure to hypoglycaemia.

Reductions in hypoglycemia in the intervention group were present across all age groups, particularly significant in those aged above 65 years, and over 24 h of the day, with benefit particularly pronounced during nighttime. Reduced nocturnal hypoglycemia likely resulted through learning from historical nighttime sensor glucose data leading to adjustments in pre-bedtime snacks or overnight basal insulin doses. Improved daytime hypoglycemia was likely achieved through a combination of on-demand access to real-time sensor glucose results with trend arrows, enabling preventative action and informing behavior modification, alongside HCP review of glucose reports with the participant, to alter the balance of insulins. Smaller, daily adjustments to insulin doses or proportions may not be apparent in the total insulin dose [29]. Given the association of hypoglycemia with adverse clinical outcome, including enhanced risk of cardiovascular events, increased hospital admissions, and reduced survival [5, 7], these results for multiple hypoglycemia-related secondary endpoints highlight the effectiveness and safety of this technology and its potential for improving glycemic control. Detection of

hypoglycemia, especially nocturnal, can be difficult with intermittent glucose monitoring even when it is performed frequently.

Once intervention participants were able to see sensor glucose readings, their blood glucose testing frequency fell to around 1 test every 3 days, with 57% of participants testing less than once every 10 days. High device utility rate (89%) [22] with average sensor scanning eight times daily replaced blood glucose testing and shows confident use of the technology to access current and historic sensor glucose data. In contrast, although the control group remained concordant with regular blood glucose testing throughout the study (averaging 3–4 tests daily), they did not benefit from a reduction in hypoglycemia.

In addition to benefiting from less time in hypoglycemia compared with the control group, intervention participants showed improvement in glucose variability [30] and LBGI, a specific risk marker for hypoglycemia [31]. These findings can be partially explained by the documented association between hypoglycemia and glucose variability [30, 31]. The reduction in hypoglycemic exposure in the intervention group may offer additional clinical benefits [8, 9].

A significant improvement in HbA1c was detected in those younger than 65 years. Although the reasons for this finding are not entirely clear we hypothesize that the convenience associated with sensor glucose readings, compared with blood glucose testing, prompted more frequent testing. This supports a recent study reporting younger participants as being "too busy" for finger-stick testing [32]. HbA1c level was unchanged for intervention participants $\geq$65 years. Again the reasons for this are not entirely clear, and we hypothesize that the benefit for older intervention participants of being able to visualize actual or potential hypoglycemic risk prompted a more cautious approach to therapy adjustments for this vulnerable group, prioritizing hypoglycemia reduction over a more indiscriminate approach to glucose control. The overall impact of these two approaches to care was no effect on HbA1c.

These findings may have future clinical implications as past studies show worse glycemic control in younger participants with type 2 diabetes [3, 4] and this new sensor-based technology may be helpful for these participants. However, no adjustments were made for multiple testing by subgroup and future work is required to confirm this observation.

Participants in the intervention group had improved quality of life and satisfaction with their treatment compared with control. The visual presentation of the historical glucose profile and ease of testing with flash glucose monitoring, avoidance of blood glucose testing, and reduced concerns about hypoglycemia probably contributed to improved quality of life and satisfaction with treatment. A recent study investigating insulin-treated participants on continuous glucose monitoring has shown, similar to our study, improved quality of life measures, attributed to various factors including reduced fear of hypoglycemia, greater confidence, and perceived control over diabetes [33].

Our study results support those of a recent randomized control trial comparing use of this technology with blood glucose testing in adults with well-controlled type 1 diabetes, which also demonstrated superior reduction in hypoglycemia without deterioration of HbA1c and improved treatment satisfaction [34]. Limitations of this work include the absence of a treatment algorithm for modifying insulin therapy. Our aim was to test the new technology in "real-world settings" according to local practices in different centers. Having restrictive protocols for treatment changes

would have made general applicability of our data uncertain. Our inclusion of only adults with intensive insulin therapy performing regular glucose testing means future studies to assess the effectiveness of this novel glucose-sensing technology in younger, less concordant, individuals with type 2 diabetes are needed. Had there been an insulin treatment algorithm and inclusion of participants with less regular blood glucose testing, the similar decline in HbA1c observed in both groups during the short period of this study may have been different. Common to glucose technology studies, our intervention was non-masked to subjects as sensor wear was experienced by all with assessment and some treatment decisions based on the same sensor glucose values [35]. No adjustment was made for multiple testing of secondary endpoints. Many of the endpoints, particularly those derived from sensor glucose values, are highly inter-related and should not be considered in isolation.

CONCLUSION

In summary, use of sensor glucose readings resulted in similar drop in HbA1c compared with standard methods of blood glucose testing. When compared with self-monitored blood glucose testing there were no safety concerns and use of this new technology was associated with highly significant reductions in hypoglycemic measures across all age groups, decreased glucose variability, and improved quality of life and treatment measures. Collectively these results demonstrate that flash glucose-sensing technology is safe and effective when used in place of standard self-monitoring of blood glucose for glycemic management of type 2 diabetes treated by intensive insulin therapy.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. TH wrote the first draft of the manuscript and together with all the co-authors worked collaboratively to write, discuss, and review this manuscript which was revised and edited by RA. All named authors collectively took the decision to submit it for publication.

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Compliance with Ethics Guidelines. Approval was given by the appropriate competent authorities in each country. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Budget Impact Analysis of a Flash Glucose Monitoring System for People with Type 2 Diabetes who are using Intensive Insulin

PMD34

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Background

- Type 2 diabetes mellitus (T2DM) is associated with a significant economic burden. In 2010–2011, the total annual cost of T2DM was estimated to be £21.8 billion in the UK (direct costs, £8.8 billion; indirect costs, £13 billion), and treating and managing complications of the disease amounted to 80% of the total direct costs.[1]
- Healthcare expenditure for the management of T2DM is escalating with the increasing prevalence of the disease.[1] In addition, use of insulin to treat T2DM is associated with higher costs compared with oral medication; a German prospective study (n = 256) found a 66% increase in resource use related to diabetes in the 6 months after initiation of insulin therapy.[2]
- The FreeStyle Libre™ system is a novel, sensor-based, factory-calibrated flash glucose monitoring system that continuously measures glucose levels in a patient's interstitial fluid. Data are wirelessly transferred from the sensor (which lasts for up to 14 days) to a handheld reader.
- The REPLACE trial was a 6-month, multicentre, randomized trial of the flash glucose monitoring system versus self-monitoring of blood glucose (SMBG) in adults with poorly controlled T2DM using intensive insulin therapy (Table 1).[3]
- In the REPLACE trial, substantial decreases in all-cause healthcare resource use were observed for people using the flash glucose monitoring system compared with people using SMBG.[3]
- By reducing healthcare resource use, the flash glucose monitoring system can potentially reduce healthcare costs for people with T2DM using intensive insulin therapy.

Objective

- A model was developed to assess the budget impact of the flash glucose monitoring system compared with SMBG from the German healthcare system perspective. The model was based on the costs of glucose monitoring and reductions in all-cause healthcare resource use observed in the REPLACE trial.

Methods

Glucose monitoring

- Costs of glucose monitoring included the acquisition costs of the flash glucose monitoring system reader and sensors, and the costs of lancets and test strips (Table 2).
- Costs were based on unit costs in Germany.
- People using SMBG alone were assumed to carry out an average of three tests per day, as observed in the REPLACE trial.
- According to the product labelling, people using the flash glucose monitoring system need to use SMBG to check flash glucose monitoring system readings: 1) during times of rapidly changing glucose levels; 2) in order to confirm hypoglycaemia or impending hypoglycaemia; and 3) if symptoms do not match the flash glucose monitoring system reading. As observed in the REPLACE trial, flash glucose monitoring system users were assumed to conduct an average of 0.3 SMBG tests per day.

Healthcare resource use

- Patients with high levels of glycated haemoglobin (HbA_{1c}) and a long duration of diabetes, such as those included in the REPLACE trial, have a high risk of developing complications which may lead to increased use of healthcare resources.[4]
- All-cause resource use is widely used in economic evaluations as disease-specific resource use is difficult to assess objectively, particularly for people with diseases such as T2DM, who are likely to have comorbidities.[5–7]
- All-cause healthcare resource use data observed in the REPLACE trial were incorporated in the model, and included resource use resulting from emergency room visits, ambulance call-outs and hospital admissions.
- Costs were based on estimated costs for Germany.
- People using the flash glucose monitoring system in the REPLACE trial used fewer healthcare resources than those using SMBG alone (Table 3).

Results

Glucose monitoring

- The total costs of glucose monitoring are estimated to be €897 higher per patient per year (PPPY) for people using the flash glucose monitoring system compared with those using SMBG alone (Table 2).

Table 1. Baseline patient characteristics in the REPLACE trial

Baseline characteristic	Flash glucose monitoring system (n = 149)	SMBG (n = 75)
MDI (pen or syringe)/CSII (insulin pump), %	94.6/5.4	94.7/5.3
Mean age, years (± SD)	59.0 (± 9.9)	59.5 (± 11.0)
Mean HbA_{1c}, % (± SD)	8.65 (± 1.01)	8.75 (± 0.98)
Mean duration of diabetes, years (± SD)	17 (± 8)	18 (± 8)
Mean duration of insulin, years (± SD)	9 (± 6)	10 (± 7)
Mean frequency of SMBG, tests per day (± SD)	3.6 (± 1.3)	3.9 (± 1.3)

CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; SD, standard deviation; SMBG, self-monitoring of blood glucose.

Table 2. Estimated glucose monitoring costs for people using the flash glucose monitoring system and for those using SMBG

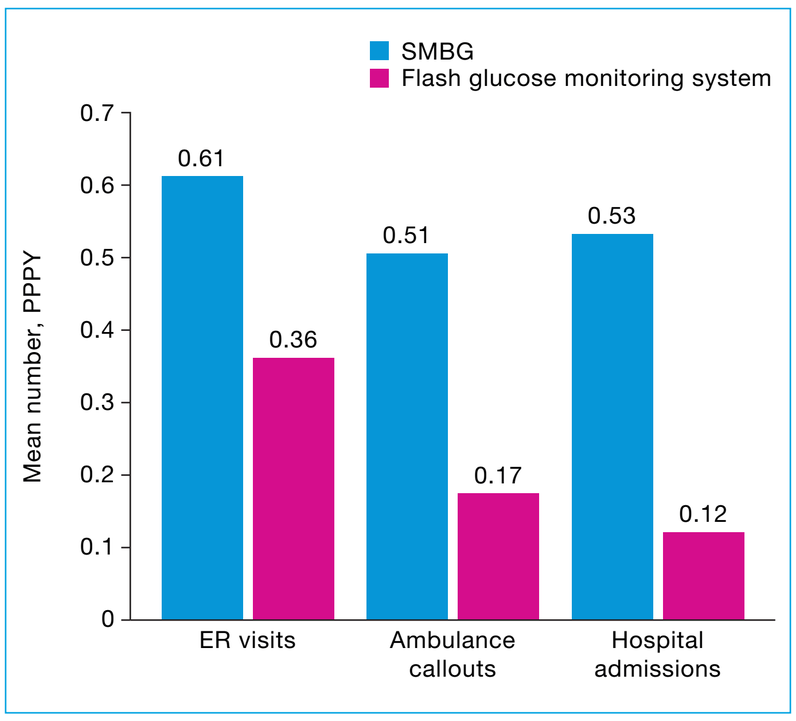
	Cost (€)
Flash glucose monitoring system	
Cost per reader	59.90
Cost per sensor	59.90
Annual cost of reader and sensor, PPPY[a]	1577.37
SMBG	
Cost per lancet[8]	0.12
Annual cost (flash glucose monitoring system users), PPPY[b]	13.14
Annual cost (routine SMBG users), PPPY[c]	131.40
Cost per test strip[9]	0.57
Annual cost (flash glucose monitoring system users), PPPY[b]	62.42
Annual cost (routine SMBG users), PPPY[c]	624.15
Estimated cost of glucose monitoring for flash glucose monitoring system users, PPPY	**1652.93**
Estimated cost of SMBG for routine SMBG users, PPPY	**755.55**
Additional cost (flash glucose monitoring vs SMBG), PPPY	**897.38**

[a]Assumption: use of 26 sensors per year (sensor life is 14 days; reader lasts for 3 years). [b]Assumption: use of 0.3 SMBG tests per day observed in the REPLACE trial. [c]Assumption: use of three SMBG tests per day observed in the REPLACE trial.
PPPY, per patient per year; SMBG, self-monitoring of blood glucose.

Healthcare resource use

- For people with T2DM using intensive insulin therapy, the flash glucose monitoring system was associated with a reduction in all-cause healthcare resource use in the REPLACE trial (Figure 1), which is estimated to amount to a €1282 reduction in healthcare resource use costs PPPY, compared with SMBG (Table 3).

Figure 1. All-cause healthcare resource use recorded in the REPLACE trial, PPPY



ER, emergency room; PPPY, per patient per year; SMBG, self-monitoring of blood glucose.

Table 3. All-cause healthcare resource use costs calculated from data observed in the REPLACE trial

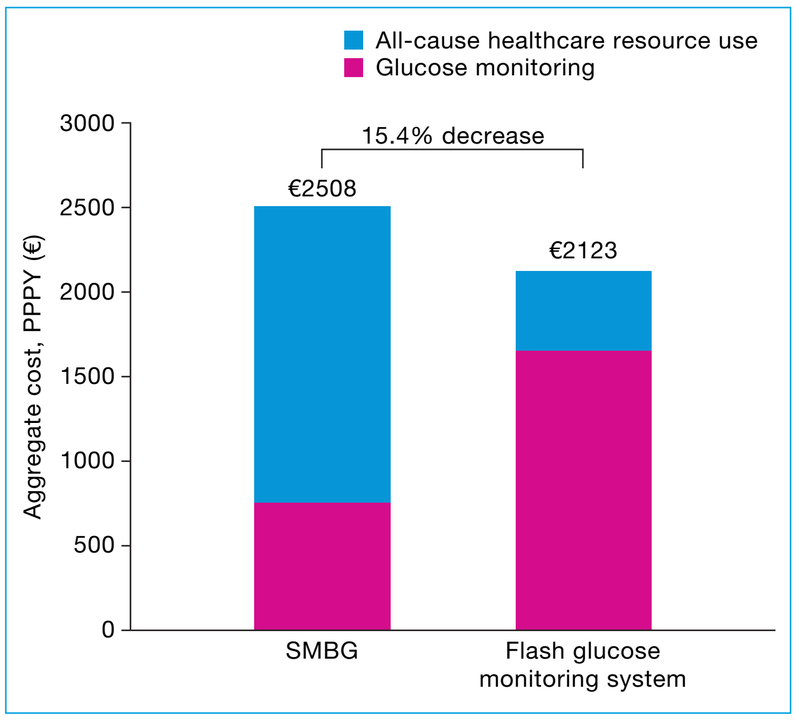
ER visits	
Cost per ER visit[10]	€127.72
ER visits, PPPY: flash glucose monitoring system	0.3624
ER visits, PPPY: SMBG	0.6134
Cost of ER visits, PPPY: flash glucose monitoring system	€46.29
Cost of ER visits, PPPY: SMBG	€78.34
Ambulance call-outs	
Cost per ambulance call-out[11]	€744.00
Ambulance call-outs, PPPY: flash glucose monitoring system	0.1744
Ambulance call-outs, PPPY: SMBG	0.5066
Cost of ambulance call-outs, PPPY: flash glucose monitoring system	€129.75
Cost of ambulance call-outs, PPPY: SMBG	€376.91
Hospital admissions	
Cost per hospital admission[12]	€2431.56
Hospital admissions, PPPY: flash glucose monitoring system	0.1208
Hospital admissions, PPPY: SMBG	0.5334
Cost of hospital admissions, PPPY: flash glucose monitoring system	€293.73
Cost of hospital admissions, PPPY: SMBG	€1296.99
Estimated cost of all-cause resource use for flash glucose monitoring system users, PPPY	**€469.77**
Estimated cost of all-cause resource use for routine SMBG users, PPPY	**€1752.25**
Reduction in costs (flash glucose monitoring system vs SMBG), PPPY	**€1282.48 (73.2% decrease)**

ER, emergency room; PPPY, per patient per year; SMBG, self-monitoring of blood glucose.

Aggregate costs of glucose monitoring and all-cause healthcare resource use

- The flash glucose monitoring system is estimated to be associated with a saving of €385 PPPY compared with SMBG; this equates to a 15.4% decrease in aggregate costs (Figure 2; Table 4).

Figure 2. Aggregate costs of glucose monitoring and all-cause healthcare resource use, PPPY



PPPY, per patient per year; SMBG, self-monitoring of blood glucose.

Table 4. Aggregate costs of glucose monitoring and all-cause healthcare resource use

	Cost (€)
Flash glucose monitoring system	
Costs of glucose monitoring and resource use, PPPY	2122.69
SMBG	
Costs of glucose monitoring and resource use, PPPY	2507.80
Reduction in costs (flash glucose monitoring system vs SMBG), PPPY	**385.11 (15.4% decrease)**

PPPY, per patient per year; SMBG, self-monitoring of blood glucose.

Conclusions

- The budget impact model calculations show that when considering aggregate costs of glucose monitoring and all-cause healthcare resource use in people with T2DM using intensive insulin therapy, the use of a flash glucose monitoring system is estimated to provide a 15.4% reduction in costs compared with SMBG, on a PPPY basis.
- These results suggest that, compared with SMBG, a flash glucose monitoring system can be considered to be more affordable and provide a potential cost-saving benefit to the German healthcare system.
- At sensor prices lower than the one used in this model, the flash glucose monitoring system would be even more affordable.
- To achieve optimal glucose control, some people with T2DM using multiple daily injections may require more than the three SMBG tests per day observed in the REPLACE trial. This is supported by the fact that people using the flash glucose monitoring system in the REPLACE trial, who had a statistically significant reduction in hypoglycaemia compared with the SMBG group, scanned a mean of eight times per day. Each additional daily SMBG test would add €252 PPPY to the cost of glucose monitoring. By contrast, there is no incremental cost of additional scans using the flash glucose monitoring system.
- The budget impact of the flash glucose monitoring system can also be assessed using low glucose events (for example < 45 mg/dL) as a proxy for severe hypoglycaemia. This approach is most suitable for populations in which the costs of hypoglycaemia are likely to outweigh the costs related to long-term complications of diabetes, such as people with well-controlled type 1 diabetes mellitus (T1DM). This model will be presented in a future publication.

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DTT

ORIGINAL ARTICLE

Factory-Calibrated Continuous Glucose Sensors: The Science Behind the Technology

Udo Hoss, PhD and Erwin Satrya Budiman, PhD

Abstract

The use of commercially available continuous glucose monitors for diabetes management requires sensor calibrations, which until recently are exclusively performed by the patient. A new development is the implementation of factory calibration for subcutaneous glucose sensors, which eliminates the need for user calibrations and the associated blood glucose tests. Factory calibration means that the calibration process is part of the sensor manufacturing process and performed under controlled laboratory conditions. The ability to move from a user calibration to factory calibration is based on several technical requirements related to sensor stability and the robustness of the sensor manufacturing process. The main advantages of factory calibration over the conventional user calibration are: (a) more convenience for the user, since no more fingersticks are required for calibration and (b) elimination of use errors related to the execution of the calibration process, which can lead to sensor inaccuracies. The FreeStyle Libre™ and FreeStyle Libre Pro™ flash continuous glucose monitoring systems are the first commercially available sensor systems using factory-calibrated sensors. For these sensor systems, no user calibrations are required throughout the sensor wear duration.

Keywords: Continuous Glucose Monitoring, Glucose sensor, Calibration, Factory calibration, Subcutaneous.

Introduction

Since the introduction of commercially available continuous glucose monitoring systems in 2000, significant progress in terms of system performance and convenience of use has been achieved, garnering positive expectation on the clinical utility and adoption of this technology.[1,2] The first system introduced by MiniMed was a retrospective system, with data being available to the user or healthcare professional at the end of the sensor wear time.[3] These early sensors could only be used for up to 3 days and needed a minimum of four calibrations per day. Over the following years the systems became easier to use, the accuracy of the systems improved, and the allowed wear duration was extended. However, until recently all systems still required daily blood glucose (BG) tests for recalibration to maintain accurate sensor glucose readings throughout sensor wear.

Most currently available continuous glucose monitoring systems employ enzymatic amperometric sensors measuring glucose in the interstitial subcutaneous tissue. The measurement signal is an electrical current. That current is proportional to the glucose concentration at the measurement site, with a small background current, which can be accounted for as a signal offset if necessary. To display glucose information to the user of the system, the sensor signal will have to be converted from an electrical current to a glucose value. This conversion is called calibration, and involves a BG test by the user. Assuming a linear sensor response to glucose and a negligible or known background signal, the sensor sensitivity to glucose can be calculated from one sensor current value and its corresponding time-matched BG reading. The sensor sensitivity represents the calibration factor, which can be used to convert the sensor electrical response into a glucose value moving forward from the calibration time point.

The user calibration process has several disadvantages. First, it is a burden to the user of the sensor system, since each calibration process requires a painful and time-consuming BG test. More importantly, the accuracy of the BG test directly determines the accuracy of the sensor system. Certain user mistakes like not washing hands before a BG test can

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lead to wrong glucose numbers. Some sensor systems require the user to enter the BG value manually for calibration, where transcription error and delayed BG entry can affect sensor accuracy. On the other side, assuming the BG test was performed correctly, if at the time of calibration the sensor signal has a temporarily falsely reduced or elevated value, for example, caused by interfering substances, the calculated sensor sensitivity will not be correct and the following sensor data will persistently be falsely reduced or elevated. An alternative to the user calibration process is sensor factory calibration, which has been implemented for the FreeStyle Libre™ and FreeStyle Libre Pro™ flash continuous glucose monitoring systems (hereafter referred to as FreeStyle Libre).

In this article, we will review data to be collected through scientific experiments to demonstrate the feasibility of factory calibration. These requirements apply to any subcutaneous glucose sensor system intended to be factory calibrated. Results obtained during the development of FreeStyle Libre are included to illustrate the type of experiments and analysis required. However, it is not the purpose of this article to provide comprehensive data demonstrating feasibility of factory calibration for the FreeStyle Libre sensor.

What is Factory Calibration?

Factory calibration of sensors removes the need for determining the sensor sensitivity from the user's responsibility and instead places it in the hands of the sensor manufacturer. The sensor sensitivity is determined during the sensor manufacturing process, and that information is included with every sensor in the form of a sensor code. That code can be preprogrammed into the sensor electronics such that no user interaction is required to enter the code, eliminating the risk of transcription error.

The factory calibration process includes the following steps:

- Manufacture sensor lots with low sensor to sensor variability.
- Sample a number of sensors from each sensor lot and test them in the laboratory (in vitro) for their response to glucose and determine their glucose sensitivity.
- Convert the lot glucose sensitivity into a sensor code.
- Program the sensor code into the sensor electronics memory.
- Demonstrate that the initially determined sensor sensitivity does not change over the sensor shelf life.

Since the variation between the sensors in one sensor lot is small, the laboratory tested sensors are representative of the remaining sensors in the sensor lot, which will be used by patients. The code information provides the necessary sensor sensitivity or calibration factor for every sensor in the sensor lot to convert the electrical sensor current into a glucose value. The determination of the code may include corrections for the difference between in vitro and in vivo sensor testing, which can be determined analytically or empirically through clinical trials, and which can be applied universally to all sensor lots.

This process determines how the sensor responds to glucose and will provide glucose data after sensor insertion without the necessity of a BG test by the user. It does, however, by itself not remove the requirement for recalibrations during sensor wear. To avoid recalibrations, it is necessary that the assigned sensor sensitivity remains valid throughout the sensor wear. This is a requirement related to both the sensor chemistry as well as the sensor biocompatibility.

The term factory calibration refers by itself only to the process of determining the initial sensor sensitivity during the manufacturing process. However, it is widely understood and expected that factory-calibrated sensors do not require any calibrations by the user, including no recalibrations during sensor wear.

To be able to provide factory-calibrated sensors to the user there is a set of requirements beyond the general requirements shared among glucose sensors,[4] as outlined in Table 1.

The first three requirements are related to the design and manufacturing of the sensor and the chemistry involved, whereas the last requirement depends on the biology of the interstitial tissue.

With respect to consistency of the sensor manufacturing process, it is important to identify the sensor components which do affect its sensitivity. For an amperometric sensor, the sensing area located on the working electrode containing the enzyme and the membrane covering the enzyme and limiting the flux of glucose from the tissue to the enzyme are the critical components. Therefore, it is essential to develop processes to reproducibly deposit the enzyme on the working electrode and to create a uniform coating of the glucose-limiting membrane. Variations in sensing layer area and membrane thickness between sensors have to be kept small, which requires a high-precision manufacturing equipment given that the areas involved are in the range of less than 1 mm^2 and the membrane thickness is typically less than 100 μm. Sensor design and architecture determine the options for manufacturing methods. Therefore, if factory calibration is the goal, it is crucial that these limitations are taken into consideration early in the development process, so that the sensor architecture will allow the use of robust manufacturing processes.

The sensor sensitivity is determined as part of the factory calibration process at the end of the sensor manufacturing process. This information is assigned to every individual sensor usually in the form of a code. However, sensors are not being used immediately after they are produced, and there will be a period of time between the production and the use date. During that time the sensor sensitivity cannot change. Otherwise, the initially assigned sensitivity is no longer valid and the sensor will provide false data once inserted and used by the patient.

Table 1. Requirements for Factory Calibration

Requirement	*Objective*	*Testing environment*
Consistent sensor manufacturing	Reduce sensitivity variation between sensors.	In vitro
Shelf life stability	Maintain sensor sensitivity over the assigned shelf life.	In vitro
Wear stability	Maintain sensor sensitivity over the wear duration.	In vitro/ in vivo
Consistent blood/tissue relationship	Demonstrate consistent BG-to-ISF-glucose gradient between subjects.	In vivo

BG, blood glucose.

Similar to the requirement that the sensor needs to be stable over its assigned shelf life, it also needs to be stable over its use period.[5] If the sensitivity of the sensor to glucose does not change over the wear time, then recalibrations are not necessary. Alternatively, if the sensor response does change, recalibrations by the user can compensate for that sensor drift. Sensor drift is the reason why all currently available sensor systems, except FreeStyle Libre, require BG-based fingerstick calibrations by the user, typically twice a day.

The sensor stability over its use period is determined by two fundamentally different sensor properties. The first is the ability of the sensor to detect glucose with a stable sensor response. This property is governed by the underlying sensor chemistry and the enzyme involved, and can be demonstrated through in vitro tests. The second property is related to the biocompatibility of the sensor. The foreign body response to the sensor inserted into the subcutaneous tissue may lead to a change in sensor response.[6] Therefore, to keep the signal stable over the wear period, the sensor design and the membrane chemistry either have to minimize the foreign body response or be able to prevent that response from interfering with the sensor signal. The sensor stability in vivo has to be determined through clinical trials.

The last requirement for the feasibility of factory calibration is the only requirement that is not related to the sensor itself. Since the currently available sensor systems are measuring glucose in the interstitial fluid, but are expected to predict the BG concentration, a consistent ratio between blood and tissue glucose is required. Many studies have been performed to estimate the absolute value of the interstitial glucose concentration and its relationship to BG. No clear consensus has been achieved to date,[7] but most recent publications tend to estimate the tissue glucose to be around 90% of BG under steady-state conditions.[8] However, most studies only report an average value and attribute any variations to the experimental conditions and errors. Therefore, data need to be generated with respect to the variation of the blood to tissue glucose ratio variation both within a subject at different body sites or between different subjects.

The accuracy of a factory-calibrated sensor system will depend on the variations of the parameters associated with the requirements in Table 1. For example, minimizing the variation in sensitivity from sensor to sensor through manufacturing controls will minimize the sensor performance variance from individual to individual. The overall accuracy of the factory-calibrated sensor is achieved by applying appropriate specifications for the requirements in Table 1. Each specification will impact the accuracy independently, and therefore, it is up to the manufacturer to choose a set of specifications which will guarantee a desired accuracy level.

Implementation of Factory Calibration for FreeStyle Libre

The FreeStyle Libre and FreeStyle Libre Pro flash continuous glucose monitoring systems are the first commercially available factory-calibrated sensor systems. To our knowledge, no scientific studies have been published previously evaluating the feasibility of factory calibration besides the ones leading to FreeStyle Libre.[9–13] All calibration-related studies and publications were focused on understanding and improving the standard BG-based fingerstick calibration[14–30] or overcoming transient effects, such as lag and signal artifacts[31–35] that can impact calibration. This demonstrates the novelty of this alternative approach and also possibly the superiority of the chemistry used in FreeStyle Libre over other sensor systems.

The development of the FreeStyle Libre sensor was guided by the requirements as outlined in Table 1. The chemistry as well as the architecture of the sensor was optimized to provide the necessary stability and robustness.

The FreeStyle Libre sensor is an enzymatic amperometric 3-electrode sensor system. The chemistry is based on the Wired Enzyme technology, which has been utilized in the FreeStyle Navigator continuous glucose monitoring system. This technique uses mediator molecules which are crosslinked together with the enzyme into a polymer matrix. Glucose molecules diffuse from the interstitial tissue through the outer membrane into the enzyme matrix and are oxidized by the enzyme glucose oxidase. The resulting electrons are transferred from the enzyme to mediator molecules (an osmium complex) and then shuttled to the working electrode using neighboring mediator molecules. The required electrical potential at the working electrode is only 40 mV versus a Ag/AgCl reference electrode. A low electrical potential minimizes the oxidation of electroactive species at the working electrode and thereby minimizes susceptibility to interferents.[36–38]

The sensor design and the related manufacturing processes for the FreeStyle Libre sensor were chosen specifically to be able to manufacture identical sensors with respect to their response to glucose (Table 1). The most critical elements are the sensing layer containing the enzyme and the glucose limiting membrane. The manufacturing equipment applying these two components has been optimized for robustness and reproducibility. Additional inspection steps ensure that every single sensor meets the predetermined specification criteria. Sensor lot release testing provides the lot calibration code and also includes a quantitative measure of within-lot variability.

The factory calibration process is based on the assumption that the in vitro sensor sensitivity predicts the in vivo sensor response. Since the sensor measurement site is the interstitial fluid and the reported value is BG, it is required to establish the relationship between the glucose concentrations of these two compartments. This can be done analytically or empirically. The analytical path will take into account all factors which are different in vitro versus in vivo, and which do influence the sensor response, for example, absolute glucose concentration, temperature, oxygen, and interfering substances. Alternatively, the in vitro to in vivo relationship can be established empirically by performing clinical studies and comparing the in vivo response to the in vitro data.

For example, the in vitro sensitivity can be calculated by examining the signal response of a sample of sensors from a lot to a set of known glucose concentrations, and then calculating the in vitro glucose sensitivity for each sensor. The nominal in vitro sensitivity of that sensor lot is then determined by taking the mean of the per-sensor in vitro sensitivities. Similarly, the in vivo sensitivity can be calculated by examining all the paired sensor/reference BG values in each sensor from a clinical study, and calculating the in vivo sensitivity for each of the sensors. Finally, the pooled in vivo sensitivity of that sensor lot is calculated by taking the mean of the per-sensor in vivo sensitivities.

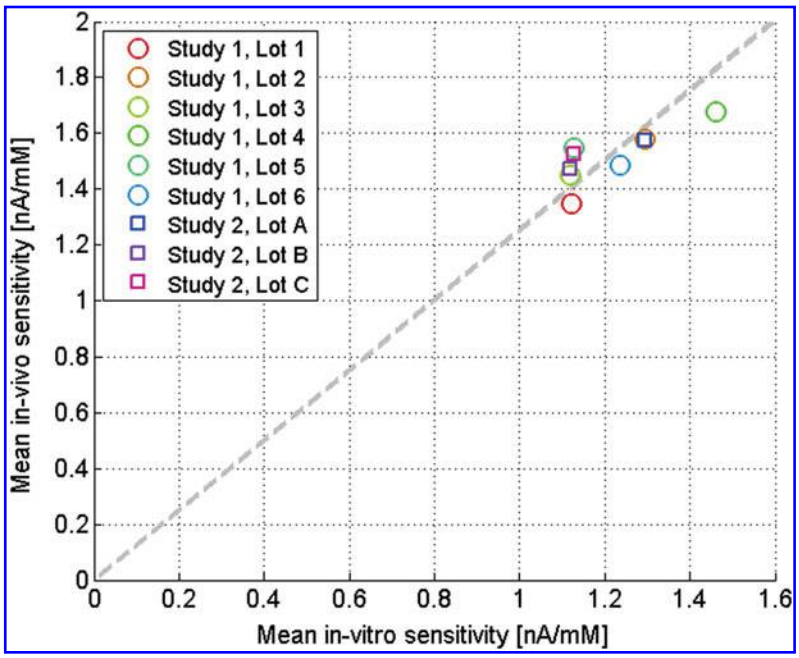

FIG. 1. Correlation between mean in vitro sensitivity and mean in vivo sensitivity of sensors from sensor lots used in Study 1 and 2. Mean in vitro sensitivity (horizontal axis) is the lot average of the individual in vitro sensor responses (sensor signal in nA divided by glucose concentration in mM). The in vitro sensor response was determined by testing sensors in glucose solution (20 mM phosphate buffered saline) with glucose concentrations ranging from 1 to 30 mM. The corresponding mean in vivo sensitivity (vertical axis) was obtained from clinical data. Individual in vivo sensor responses were calculated using capillary BG values and time paired sensor values. Correlation between in vitro and in vivo sensor sensitivity makes it possible to predict the in vivo sensor response from in vitro sensor testing (factory calibration). BG, blood glucose.

Figure 1 shows the average in vivo sensor response from multiple sensor lots compared with their in vitro sensitivity. Data shown are drawn from two separate clinical studies. One study was performed in 12 subjects with diabetes, each subject wearing three sensors from six different sensor lots simultaneously over a 5-day wear period (Fig. 1: Study 1, lot 1 through 6). The other study includes 72 subjects with diabetes,[12] each subject wore two sensors simultaneously. A total of three sensor lots were evaluated in this study (Fig. 1: Study 2, lot A through C). Capillary BG values are used as the reference BG in this analysis. While the study population and timing of the studies may have an influence on the sensitivity values and the narrow sensitivity range of the sensor lots used in the studies is limiting the statistical significance of data, we can see a correlation between the in vitro and in vivo values and an overlap of data from the two separate clinical studies.

Measuring and monitoring shelf-life stability for sensors can be performed under standard temperature conditions or under accelerated conditions at elevated temperatures. If accelerated conditions are chosen, data need to be available to determine the required exposure duration at the selected elevated temperature. These data are usually based on an Arrhenius relationship, which needs to be established for the specific sensor system. Sensor shelf life is limited by the stability of the enzyme and it is essential that the enzyme immobilization conditions are selected carefully. For the FreeStyle Libre sensor, the enzyme is immobilized in a crosslinked polymer matrix, which provides an optimized environment for enzyme stability.[39]

Sensor stability for the FreeStyle Libre sensor over its 14-day use period has been demonstrated earlier.[10] The in vitro tests include an initial sensitivity test, where the sensor is exposed to glucose solutions with different glucose concentrations. From the sensor response, a sensitivity value can be calculated. After this initial test, the sensors are kept in a glucose solution for 14 days to measure that glucose level continuously. After the 14-day period, another sensitivity test equal to the test at the beginning is being performed, and the resulting sensitivity is compared with the sensitivity at the beginning of the 14-day test. The difference between the initial and the final test represents the drift the sensor is experiencing over a 14-day monitoring period.

In vivo testing of sensor stability is absolutely required in addition to in vitro testing since different processes may be limiting stability in the tissue. In vivo stability is the ultimate requirement for sensor stability, and it may not be necessary to show in vitro stability if in vivo data are available. However, due to the significantly higher effort and cost to obtain clinical data, it is efficient to optimize sensor stability in vitro and, once the desired level of stability is achieved, only then to advance to the clinical stage.

Clinical data for 14-day stability have been shown previously using a sensor based on Wired Enzyme chemistry[10] leading to the development of FreeStyle Libre. More recently, a clinical trial has been conducted using actual FreeStyle Libre sensors to evaluate accuracy of the system over a 14-day wear period. Seventy-two subjects with diabetes wore two sensors simultaneously on the back of the upper arm. Capillary BG was measured by the subjects throughout the test using the built-in FreeStyle Precision Strip Port, and compared with the glucose value reported by the factory-calibrated sensor system. The BG readings on the built-in meter are independent of, and do not influence, sensor readings.[12]

Figure 2 shows an analysis of the 14-day stability of the sensor signal. A sensitivity value is calculated from each sensor/reference BG paired data point. For each sensor, the median of these individual sensitivity values are used to normalize data. Per-sensor normalized sensitivity values were then calculated for each day. Figure 2 shows the daily medians, interquartile ranges, and the 5th and 95th percentiles. That analysis illustrates any significant trends in the sensor sensitivity over the 14 days. We see a lower value on the first day, which is presumably related to the insertion process of the sensor and the associated trauma. From day 2 throughout day 14, the median sensor sensitivity remains

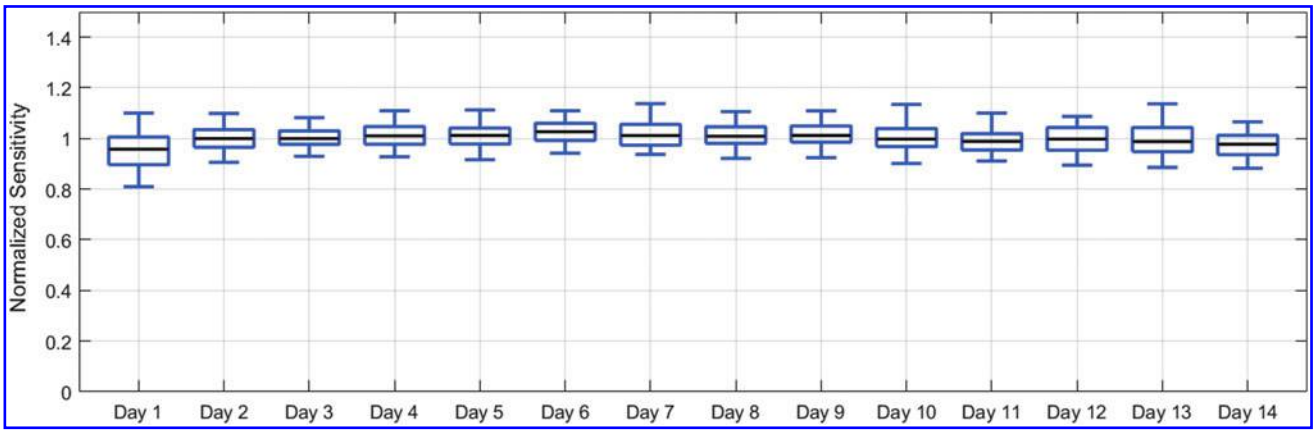

FIG. 2. Per-sensor percentile (5th, 25th, 50th, 75th, and 95th) distribution of normalized sensitivity by day. Data from 72 subjects wearing 2 sensors simultaneously were collected together with capillary BG values over a 14-day sensor wear period to calculate the in vivo sensitivities.

constant, reflecting stable sensor chemistry, as well as negligible interference from the foreign body response.

The last requirement for the feasibility of factory calibration as laid out in Table 1 is the need for a constant blood to tissue glucose relationship. This requirement can be tested by using glucose sensors with identical in vitro response to glucose in different subjects and comparing the resulting sensor sensitivities from the in vivo testing. If there was a wide distribution of the ratio of tissue to BG concentration, there would be a wide distribution of the resulting sensor sensitivities. We have previously published data supporting the hypotheses that there is no difference in the tissue to BG ratio within a person at different body sites (arm vs. abdomen) as well as between subjects.[9,11] We also used data from the clinical study described earlier[12] and analyzed the sensor data for their sensitivity variation. Sensors with a minimum wear duration of 10 days were included in the analysis. Figure 3 shows the results in a cumulative distribution function plot, separated by the three lots used in the study. We can see that the three lots have 80%–92% of their values within 10% of their respective median and 100% of the values are within 20%. There are many factors that influence the calculation of each sensor's in vivo sensitivity. Errors related to BG measurements,[40,41] transient sensor effects,[31,32,42,43] intersensor sensitivity variation used in the study, and variations in each study subject's BG range and BG rate of change range[44] can contribute to the variability observed in Figure 3. The narrow distribution indicates that the tissue to BG ratio is similar between subjects, which is required for factory calibration of sensors measuring glucose in the interstitial tissue.

Alternative Approaches to Sensor Calibration

If factory calibration is not feasible, there are other options to reduce the number of BG tests required for sensor calibration. Commercially available nonfactory calibrated continuous glucose monitoring systems require a minimum of two recalibrations per day and several studies suggest that accuracy can be impacted by increasing or decreasing this frequency.[14,20] As previously outlined, the frequency of recalibrations is determined by the stability of the sensor over the wear period. Increasing sensor stability can, therefore, allow for a reduction in recalibration frequency for example, once a day instead of twice a day.

If sensor stability can be guaranteed throughout the sensor wear time no recalibrations may be necessary, and calibration is only needed at the beginning of sensor wear. This approach has significant risk since the calibration factor applied to the sensor throughout its wear time will be determined through only one calibration event. Some sensor systems take a hybrid approach with a robust initial calibration (multiple

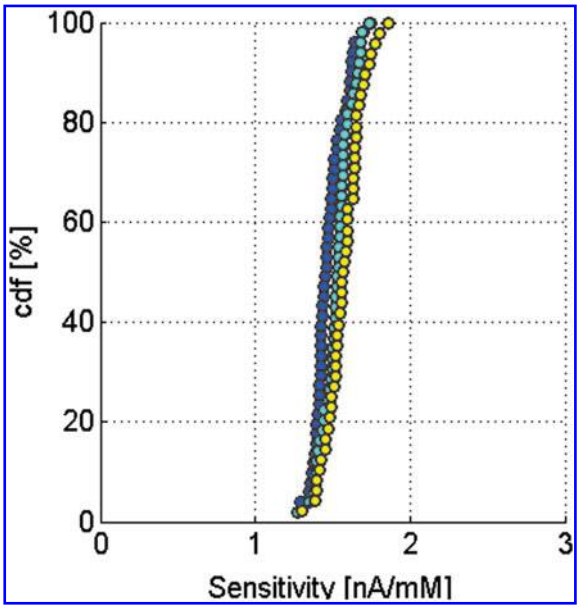

FIG. 3. Per-sensor in vivo sensitivities from three sensor lots are presented as separate distributions. Each dot represents one sensor. The in vivo sensitivity values (horizontal axis, sensor signal in nA divided by glucose concentration in mM) for the sensors are sorted from the lowest to the highest in a cumulative distribution function (cdf).The midpoint of the sorted values on the vertical axis (50th percentile) is the median value. For each of the three lots, all of the sensor sensitivities are within 20% of their corresponding median value.

fingerstick requests) and a reduced frequency of recalibrations (e.g., once every 2 days)[29,45] to minimize the overall number of BG tests required. However, many factors can impact the reliability of fingerstick calibration, resulting in calibration being one of the more dominant sources of sensor error.[22,46] In daily use, recalibration requests may be skipped or not promptly entered,[47,48] and there are many practical and technical factors[40,41,49] limiting BG accuracy.[50–53] A true factory calibration, where the sensor sensitivity is determined under laboratory conditions, is not susceptible to these use-dependent factors.

Conclusions

The availability of factory-calibrated glucose sensors has been predicted several years ago: ''… I can see the day when accuracy will be sufficient that regulators will accept that CGM values can be used for clinical decision making, that factory calibration will be possible, that reimbursement will be a foregone conclusion, and usage will be routine so that all patients and providers will need to know how to accomplish it'' (Skyler[2]). With the introduction of the FreeStyle Libre flash continuous glucose monitoring system, part of this vision has become a reality. There is no need for the user to perform BG tests for sensor calibration. Calibrations performed by the user are not only a hassle and painful, but they introduce additional cost and can also lead to inaccurate sensor readings if done incorrectly. Factory calibration is performed under laboratory conditions and is part of the sensor manufacturing process. However, to be able to implement factory calibration several requirements related to sensor stability and reproducibility have to be demonstrated and maintained over the product life.

Author Disclosures Statement

U.H. and E.B. are employees of Abbott Diabetes Care.

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Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial

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Summary

Background Tight control of blood glucose in type 1 diabetes delays onset of macrovascular and microvascular diabetic complications; however, glucose levels need to be closely monitored to prevent hypoglycaemia. We aimed to assess whether a factory-calibrated, sensor-based, flash glucose-monitoring system compared with self-monitored glucose testing reduced exposure to hypoglycaemia in patients with type 1 diabetes.

Method In this multicentre, prospective, non-masked, randomised controlled trial, we enrolled adult patients with well controlled type 1 diabetes (HbA_{1c} ≤58 mmol/mol [7·5%]) from 23 European diabetes centres. After 2 weeks of all participants wearing the blinded sensor, those with readings for at least 50% of the period were randomly assigned (1:1) to flash sensor-based glucose monitoring (intervention group) or to self-monitoring of blood glucose with capillary strips (control group). Randomisation was done centrally using the biased-coin minimisation method dependent on study centre and type of insulin administration. Participants, investigators, and study staff were not masked to group allocation. The primary outcome was change in time in hypoglycaemia (<3·9 mmol/L [70 mg/dL]) between baseline and 6 months in the full analysis set (all participants randomised; excluding those who had a positive pregnancy test during the study). This trial was registered with ClinicalTrials.gov, number NCT02232698.

Findings Between Sept 4, 2014, and Feb 12, 2015, we enrolled 328 participants. After the screening and baseline phase, 120 participants were randomly assigned to the intervention group and 121 to the control group, with outcomes being evaluated in 119 and 120, respectively. Mean time in hypoglycaemia changed from 3·38 h/day at baseline to 2·03 h/day at 6 months (baseline adjusted mean change −1·39) in the intervention group, and from 3·44 h/day to 3·27 h/day in the control group (−0·14); with the between-group difference of −1·24 (SE 0·239; p<0·0001), equating to a 38% reduction in time in hypoglycaemia in the intervention group. No device-related hypoglycaemia or safety issues were reported. 13 adverse events were reported by ten participants related to the sensor—four of allergy events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-site symptom (severe); two erythema (one severe, one mild); and one oedema (moderate). There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device.

Interpretation Novel flash glucose testing reduced the time adults with well controlled type 1 diabetes spent in hypoglycaemia. Future studies are needed to assess the effectiveness of this technology in patients with less well controlled diabetes and in younger age groups.

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Introduction

Tight glucose control and near-normal blood glucose concentrations delay the onset and progression of diabetic microvascular and macrovascular complications.[1,2] However, many patients do not achieve optimum glycaemic targets because of increased hypoglycaemia[1] and those attaining their glycaemic goals remain persistently at risk of low glucose concentrations.[3] Population-based data indicate that 30–40% of people with type 1 diabetes experience an average of one to three episodes of severe hypoglycaemia each year.[4] Nocturnal hypoglycaemia is particularly dangerous and accounts for approximately half of severe hypoglycaemic events.[5] Hypoglycaemia affects wellbeing and quality of life. A further concern is that recurrent exposure to hypoglycaemia might lead to attenuated hormonal responses to falling glucose concentrations, and ultimately impaired awareness of hypoglycaemia (hypoglycaemia-associated autonomic failure), which is associated with a several-fold increased risk of severe hypoglycaemia.[6]

A reduction of 30% or higher in hypoglycaemia is considered clinically relevant[7]; structured patient education, individualised targets, and self-monitoring of blood glucose are cornerstones in treatment to prevent and manage hypoglycaemic risk. Over the past decade, the introduction of continuous glucose monitoring to facilitate self-management has shown improved glucose control and reduced exposure to hypoglycaemia,[8] favourable findings being especially noticeable when continuous glucose monitoring has been used in sensor-augmented pump therapy[9,10] and with low-glucose suspend systems.[11] However, there are some limitations

Research in context

Evidence before this study

We searched PubMed for any studies published in English up to May 25, 2016, using flash glucose monitoring technology. Our search terms were "flash glucose monitoring" and "blood glucose". Continuous glucose monitoring was not included as a search term because of differences in the technology and expected differences in terms of patient engagement with the technology and its features. Of the 12 search results, one clinical trial was identified that compared the accuracy of the flash glucose monitoring system with capillary blood glucose. The trial reported that the factory-calibrated flash glucose monitoring system showed good accuracy, sustained over 14 days, with mean absolute relative difference of 11·4% compared with capillary blood glucose monitoring.

Interpretation

There is a gap in published data related to assessing the impact of this technology on glycaemic control. To the best of our knowledge, this is the first randomised controlled trial that has compared the effect of new flash glucose monitoring technology to self-monitoring of blood glucose on hypoglycaemia in type 1 diabetes.

Implications of all the available evidence

Our findings showed that replacing self-monitoring of blood glucose with novel flash sensor-based glucose monitoring demonstrated superior reduction in time in hypoglycaemia without deterioration of glycated haemoglobin. This novel technology could empower individuals with type 1 diabetes by providing a potential alternative to conventional self-monitoring of blood glucose testing.

with current continuous glucose monitoring devices, including relatively short sensor lifetime and daily self-monitoring of blood glucose for device calibration to ensure sensor accuracy, which have restricted their widespread use.[12]

We used a novel sensor-based flash glucose monitoring system (Freestyle Libre; Abbott Diabetes Care, Witney, Oxon, UK). The sensor is calibrated in the factory and needs no calibration during the 14 day wear. Data are transferred to the reader when it is brought into close proximity to the sensor, which then displays current sensor glucose level, a glucose trend arrow, and glucose readings over the preceding 8 h. Scanning can be done as often as is needed for current glucose concentration; otherwise, glucose data are automatically captured and stored on the sensor (every 15 min). The reader stores data for 90 days. Data can be uploaded from the reader, using the device software[13] to generate summary glucose reports (including ambulatory glucose profile) that can be reviewed by the patient alone or with their clinician. In this randomised controlled trial, we aimed to assess the efficacy of this new flash glucose monitoring technology system compared with conventional self-monitoring of blood glucose testing to prevent hypoglycaemia in adults with well controlled type 1 diabetes.

See Online for appendix

Methods

Study design and participants

We conducted this prospective, non-masked, randomised controlled study at 23 European diabetes centres (three in Sweden, six in Austria, five in Germany, three in Spain, and six in the Netherlands; the protocol is online). We enrolled participants aged 18 years or older who had been diagnosed with type 1 diabetes for 5 years or longer, had been on their current insulin regimen for at least 3 months before study entry, had a screening HbA_{1c} concentration of 58 mmol/mol (7·5%) or lower, reported self-monitoring of blood glucose levels on a regular basis (equivalent to ≥3 times a day) for 2 months or more before study entry, and were considered by the investigator to be technically capable of using the flash sensor-based glucose monitoring system. Any potentially eligible patient from the general diabetes population at each study site was invited to participate in the study (appendix p 1).

For the **protocol** see https://www.abbottdiabetescare.com/downloads/ADC-CI-APO.pdf

Patients were not included if they were currently diagnosed with hypoglycaemia unawareness; had diabetic ketoacidosis or myocardial infarction in the preceding 6 months; had known allergy to medical-grade adhesives; had used continuous glucose monitoring within the preceding 4 months; were currently using sensor-augmented pump therapy; were pregnant or were planning pregnancy; or were receiving oral steroid therapy for any disorders.

Approval was given by the appropriate competent authority in each country. All participating centres gave ethics approval before the study. Participants gave written informed consent. Original data are stored at each study centre.

Randomisation and masking

Participants were randomly assigned to flash sensor-based glucose monitoring (intervention group) or to self-monitoring of blood glucose (control group) in a 1:1 ratio by central interactive web response system (IWRS) using the biased-coin minimisation method; study centre and type of insulin administration were prognostic factors. Participants, investigators, and study staff were not masked to group allocation.

Procedures

At screening and enrolment, all participants had baseline HbA_{1c} samples measured (analysed by a central laboratory [ICON Laboratories, Dublin, Ireland]),

physical measures recorded (eg, blood pressure), and baseline values recorded for all questionnaire types. Questionnaires administered included Diabetes Distress Scale (DDS),[14] Diabetes Quality of Life Questionnaire (DQoL),[15] Diabetes Treatment Satisfaction Questionnaire (DTSQ),[16] Hypoglycaemia Fear Survey (HFS),[17] and a hypoglycaemia patient questionnaire[7] (used to record baseline perception of hypoglycaemia).

All participants wore a FreeStyle Libre device locked into masked mode for the 14 day baseline period; sensor glucose measurements were not visible to the participant or the investigator during this time (blinded). After randomisation, sensor data for participants in the intervention group were made available to them and the investigators. Glucose management was supported by self-monitoring of blood glucose, using the strip port built into the reader and compatible test strips (Abbott Diabetes Care, Witney, Oxon, UK). Participants were asked to record capillary glucose concentrations in a glucose diary and to log other events (eg, severe hypoglycaemia, hospitalisation, and additional health visits or treatment) in an event diary. Participants with sensor data for at least 50% of the blinded wear period (or ≥650 individual sensor readings) were then centrally randomised to the two groups.

After randomisation, the device was unblinded for participants in the intervention group who then continuously used sensor glucose data as per the device labelling for self-management of glucose throughout the duration of the study (6 months). Participants in the intervention group were given access to the device software, which they could use at home to review their sensor data if they wished. No training was provided to these participants for interpretation of glucose-sensor data.

Participants in the control group self-monitored glucose concentrations using the FreeStyle Lite meter and test strips (Abbott Diabetes Care, Witney, Oxon, UK). In the 14 days preceding the 3 month and 6 month time-points (days 91 and 194, respectively), participants in the control group wore the flash sensor while continuing to manage their diabetes with self-monitoring of blood glucose. All sensor glucose data were blinded for both participants and investigators.

No standardised treatment protocols or insulin titration algorithms were used in the trial. In line with standard diabetes care, all participants were encouraged to self-manage using current or historical glucose data to optimise glucose control. At clinic visits glycaemic control and glucose readings for both groups and sensor data reports using the software for participants assigned to the

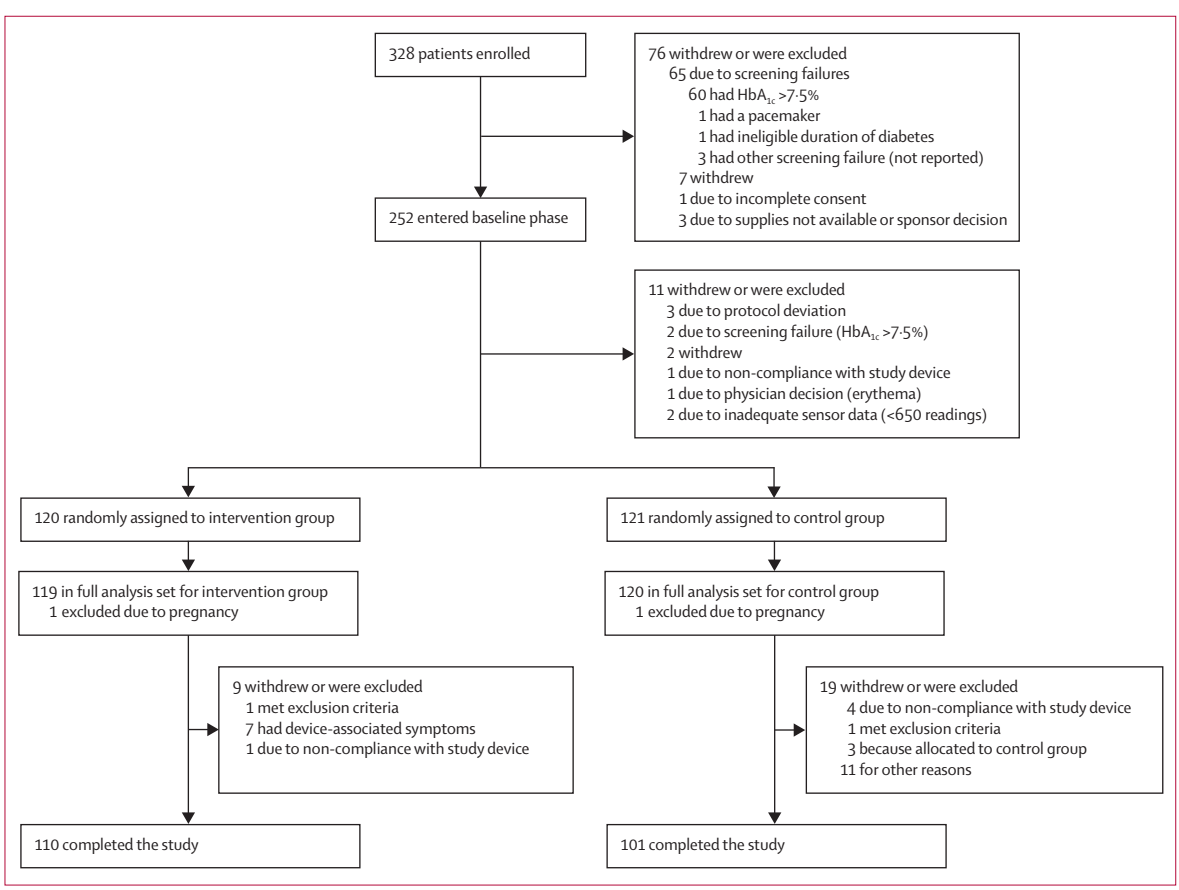

Figure 1: **Trial profile**

intervention group were formally reviewed with a health-care professional for personalised glucose management. Blood tests and physical measures were also taken at clinic visits. Questionnaires for the patient-reported outcomes were administered at the day 208 clinic visit.

Outcomes

The primary effectiveness endpoint was time spent in hypoglycaemia (<3·9 mmol/L [<70 mg/dL])[7] for the 14 days preceeding the end of the 6 month study period (days 194–208). Prespecified secondary endpoints were sensor-derived glycaemic measures at days 194–208, day 208 HbA_{1c} concentrations, change in total daily dose of insulin from day 1 to day 208; system utilisation for days 15–208 (defined as the percentage of data collected, assuming continuous device wear), and frequency of glucose finger-sticks and sensor scans per day during the study period. Sensor-derived glycaemic measures comprised: number and duration of hypoglycaemic episodes (sensor glucose <3·9 mmol/L in 24 h, by day [0600–2300 h], and night [2300–0600 h]; <3·1 mmol/L in 24 h, and <2·2 mmol/L in 24 h [<70 mg/dL, <55 mg/dL, and <40 mg/dL, respectively]; an episode was defined as at least two consecutive readings, at 15 min intervals, outside the predefined glucose range, the end of an episode was one reading at or higher than the threshold); time with glucose in range 3·9–10·0 mmol/L (70–180 mg/dL); number and duration of hyperglycaemic episodes (>10·0 mmol/L and >13·3 mmol/L [>180 mg/dL and >240 mg/dL, respectively]); and glucose variability measurements.[18] Additional outcomes assessed in the clinical study report were proportion of participants who achieve time spent in hypoglycaemia (<3·9 mmol/L; <70 mg/dL) ≤1 h/day; number of events of symptomatic hypoglycaemia; post prandial hyperglycaemia (>10·0 mmol/L, 180 mg/dL); prandial to basal insulin ratio; number of participants changing from once daily to twice daily basal insulin; body weight and body-mass index (BMI); fasting cholesterol and triglycerides; blood pressure; emergency room visits or admissions and non-protocol related additional clinic time; and medication usage (non-insulin related, including glucagon, self-reported from event diary).

Questionnaire results for the user questionnaire (participant [intervention group only] and health-care professional facing) were assessed at 6 months, with patient-recorded outcome measures (with the HFS, DTSQ, DDS, and DQoL) were assessed at baseline and at 6 months. Adverse events and sensor insertion-site symptoms were monitored throughout the study. Additionally, number of episodes of diabetic ketoacidosis and number of severe hypoglycaemia events[7] (requiring third-party assistance) were assessed and compared across the two study groups.

	Intervention (n=119)	Control (n=120)
Men	77 (65%)*	59 (49%)*
Women	42 (35%)	61 (51%)
Race		
White	119 (100%)	119 (99%)
Black	0	1 (1%)
Age (years)	42 (33–51)	45 (33–57)
BMI (kg/m²)	25·2 (3·6)	24·8 (3·5)
Duration of diabetes (years)	20 (13–27)	20 (12–32)
Screening HbA_{1c} (%; mmol/mol)	6·7 (0·5); 50·1 (5·7)	6·7(0·6); 50·2 (6·5)
Self-reported blood glucose frequency per day	5·4 (2·0)	5·6 (2·3)
Insulin administration method		
Multiple daily injections	81 (68%)	80 (67%)
Continuous subcutaneous insulin infusion	38 (32%)	40 (33%)
Insulin, total daily dose		
Basal (units)	25·7 (13·9)	20·9 (10·0)
Bolus (units)	24·2 (13·5)	22·2 (13·4)
Continuous subcutaneous insulin infusion (units)	41·4 (17·1)	35·9 (15·6)

Data are n (%), median (IQR), or mean (SD). *p=0·0153.

***Table 1*: Baseline characteristics**

Statistical analysis

We calculated that a sample size of 178 participants was needed to provide 80% power to detect a difference of 30% between groups for the primary endpoint, with a two-sided significance level of 0·05. The primary endpoint and all secondary endpoints were assessed in the full analysis set, which included all randomised participants apart from those who had a positive pregnancy test during the study period. Safety outcomes were analysed in all participants who were enrolled.

We assessed the primary endpoint using analysis of covariance comparing treatment groups with study centre, insulin administration method, and baseline time in hypoglycaemia as covariates. Missing values were imputed by last observation carried forward. This included the baseline value if no measurements after baseline were available. Changes in patient-reported outcome measures and quality of life were calculated by comparing scores from control and intervention group participants using analysis of covariance on baseline values, study centre, and insulin administration method. Confidence intervals were calculated for the group least-square mean of each measure and the difference between group least-square means.

Data analysis was performed by a contract research organisation (ICON; Dublin, Ireland), managed by Abbott Diabetes Care, and by Abbott Diabetes Care. We used SAS version 9.2 or higher for all analyses. The trial is registered with ClinicalTrials.gov, number NCT02232698.

Role of the funding source

The sponsor designed the study protocol in collaboration with the principal investigator in each country and provided all the study materials. The sponsor was

involved in collecting data and reporting results, but was not involved in the authors' interpretation or in writing text. The sponsor also funded medical writing services and gave approval to submit for publication. The corresponding author had full access to all the data in the study and, together with all authors, had final responsibility for the decision to submit for publication.

Results

We enrolled 328 participants between Sept 4, 2014, and Feb 12, 2015; 241 were subsequently randomly assigned to the intervention group (n=120) or control group (n=121) after completing the baseline phase (figure 1, table 1). The full analysis set included 239 randomised participants; one woman from each group was excluded due to pregnancy.

Time in hypoglycaemia (<3·9 mmol/L) changed from 3·38 h/day to 2·03 h/day in the intervention group (baseline adjusted mean change –1·39), and from 3·44 h/day to 3·27 h/day in the control group (baseline adjusted mean change –0·14). The adjusted between-group difference of –1·24 (SE 0·239 h/day) was highly significant (p<0·0001), equating to a 38% reduction in time in hypoglycaemia in the intervention group compared with the control group (figure 2; table 2).

The between-group differences for time in hypoglycaemia defined as sensor glucose lower than 3·1 mmol/L, 2·5 mmol/L, and 2·2 mmol/L were significant in favour of the intervention group (figure 2, table 2). The number of hypoglycaemic events registered at each hypoglycaemic threshold was significantly reduced (table 2).

Analysis by day and night showed that time below all hypoglycaemic thresholds and number of episodes were significantly improved in the intervention group compared with control (table 2, appendix pp 2–3). The between-group differences for AUC were also significant (table 2). At 6 months, 77 (65%) of the intervention group compared with 39 (33%) of the control group reduced their time in hypoglycaemia (<3·9 mmol/L) by at least 30% (p<0·0001). Time spent in hypoglycaemia was reduced almost immediately as sensor-based results became visible to participants (ie, before sensor results were reviewed with their clinician at study visits; figure 3).

Time spent in hyperglycaemia (>13·3 mmol/L) was reduced more in the intervention group than in the control group (table 2). There was no effect on time with sensor glucose concentrations higher than 10·0 mmol/L (appendix p 5). Time in range of sensor glucose 3·9–10·0 mmol/L was significantly increased in the intervention group compared with the control group at 6 months (table 2, figure 2B). Mean sensor glucose remained unchanged. Similar glycaemic data were observed after 3 months (appendix pp 6–7).

At 6 months, HbA_{1c} concentrations in the intervention group were essentially unchanged compared with the control group (table 2). There were significant between-group differences favouring the intervention group compared with the control group in the glycaemic variability measures of glucose standard deviation, mean amplitude of glycaemic excursions, low blood glucose index, and blood glucose risk index, and in continuous overall net glycaemic action results (table 2, appendix p 8).

The mean number of self-monitored blood glucose tests performed per day by the intervention group immediately reduced from 5·5 (SD 2·0) tests per day in the 14 day baseline phase to 0·5 (0·7) tests per day during the treatment phase of the trial (figure 4A). This was an unprompted response by intervention participants that clinically equates to one self-monitoring of blood glucose test every 2–5 days. The mean number of sensor scans per day for the intervention group was 15·1 (SD 6·9) during the treatment phase (figure 4A), the pattern of daily scanning is in figure 4B. System utilisation, defined as the percentage of data collected, assuming continuous device wear for 6 months by the intervention group (n=112) was 92·8% (SD 7·3). The number of self-monitoring blood glucose tests performed by participants

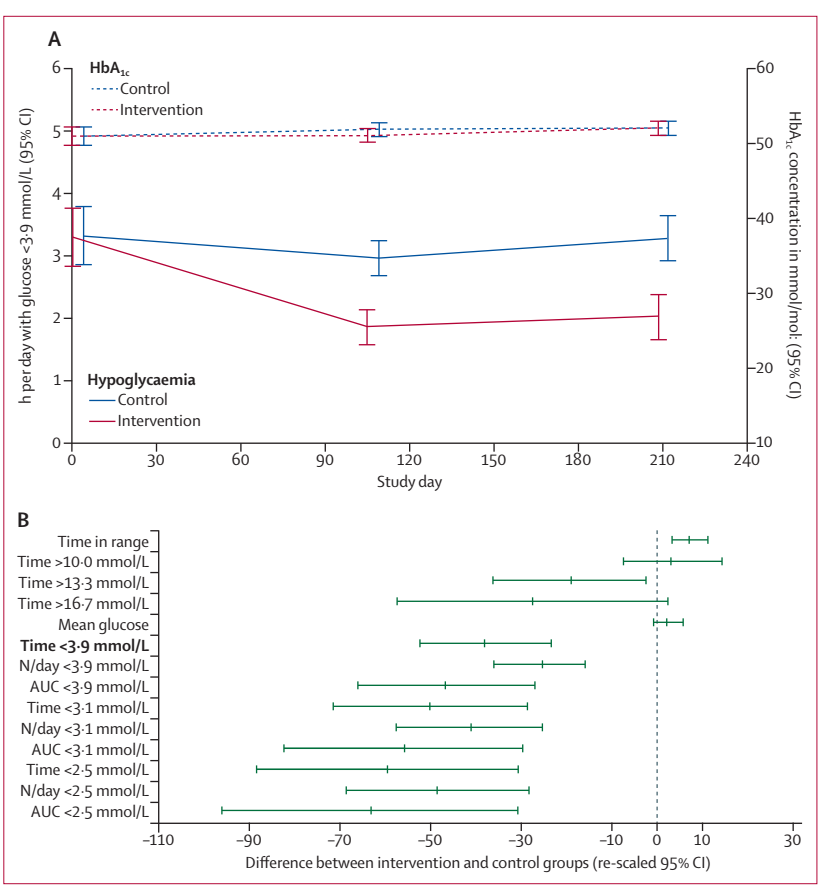

Figure 2: **Difference in groups for changes in time with hypoglycaemia and HbA_{1c} (A) and with glucose higher or lower than glycaemic thresholds (B)**

In A, control and intervention study day offset for clarity. In B, re-scaled confidence intervals are confidence intervals for the difference in the intervention group from the control group at 6 months expressed as a percentage of the control group adjusted mean.

	Baseline		Study end		Difference in adjusted means in intervention *vs* control	Difference in intervention *vs* control (%)	p value
	Intervention (n=119)	Control (n=119)	Intervention (n=119)	Control (n=119)			
HbA_{1c} (mmol/mol)	50·7 (5·7)	50·6 (7·0)	52·4 (7·2)	52·4 (7·2)	0·0 (0·65)	NA	0·9543
HbA_{1c} (%)	6·79 (0·52)	6·78 (0·64)	6·94 (0·65)	6·95 (0·66)	0·00 (0·059)	NA	0·9556
Time with glucose 3·9–10·0 mmol/L (70–180 mg/dL) in h	15·0 (2·5)	14·8 (2·8)	15·8 (2·9)	14·6 (2·9)	1·0 (0·30)	NA	0·0006
Glucose <3·9 mmol/L (70 mg/dL) within 24 h							
Events	1·81 (0·90)	1·67 (0·80)	1·32 (0·81)	1·69 (0·83)	−0·45 (0·089)	−25·8%	<0·0001
Time in h	3·38 (2·31)	3·44 (2·62)	2·03 (1·93)	3·27 (2·58)	−1·24 (0·239)	−38·0%	<0·0001
AUC (h×mg/dL)	53·42 (43·46)	58·34 (57·22)	28·58 (31·15)	54·67 (60·08)	−25·14 (5·32)	−46·7	<0·0001
Glucose <3·9 mmol/L (70 mg/dL) at night (2300–0600 h) within 7 h							
Events	0·47 (0·32)	0·46 (0·29)	0·27 (0·23)	0·40 (0·29)	−0·14 (0·029)	−33·2%	<0·0001
Time in h	1·32 (1·07)	1·48 (1·29)	0·68 (0·97)	1·23 (1·10)	−0·47 (0·118)	−39·8%	<0·0001
Glucose <3·1 mmol/L (55 mg/dL) within 24 h							
Events	0·96 (0·65)	0·92 (0·73)	0·56 (0·55)	0·92 (0·74)	−0·38 (0·074)	−41·3%	<0·0001
Time in h	1·59 (1·42)	1·77 (1·86)	0·80 (0·96)	1·65 (1·97)	−0·82 (0·175)	−50·3%	<0·0001
AUC (h×mg/dL)	16·04 (17·46)	18·94 (23·22)	7·59 (10·25)	17·69 (26·34)	−9·67 (2·29)	−56·1%	<0·0001
Glucose <3·1 mmol/L (55 mg/dL) at night (2300–0600 h) within 7 h							
Events	0·34 (0·27)	0·36 (0·34)	0·19 (0·24)	0·30 (0·28)	−0·11 (0·03)	−34·9%	0·0005
Time in h	0·62 (0·60)	0·75 (0·83)	0·31 (0·43)	0·66 (0·080)	−0·32 (0·07)	−48·9%	<0·0001
Glucose <2·5 mmol/L (45 mg/dL) within 24 h*							
Events	0·56 (0·52)	0·59 (0·60)	0·29 (0·36)	0·56 (0·59)	−0·26 (0·06)	−48·5%	<0·0001
Time in h	0·85 (1·03)	1·04 (1·36)	0·38 (0·58)	0·96 (1·57)	−0·55 (0·14)	−59·5%	<0·0001
AUC (h×mg/dL)	3·99 (5·36)	5·00 (7·10)	1·74 (2·91)	4·73 (8·66)	−2·88 (0·75)	−63·1	0·0002
Glucose <2·5 mmol/L (45 mg/dL) at night (2300–0600 h) within 7 h*							
Events	0·23 (0·23)	0·27 (0·31)	0·11 (0·16)	0·21 (0·22)	−0·09 (0·02)	−44·9%	<0·0001
Time in h	0·36 (0·44)	0·48 (0·66)	0·15 (0·25)	0·43 (0·65)	−0·25 (0·06)	−60·4%	<0·0001
Glucose <2·2 mmol/L (40 mg/dL) within 24 h							
Events	0·39 (0·43)	0·44 (0·51)	0·19 (0·29)	0·43 (0·55)	−0·22 (0·050)	−55·0%	<0·0001
Time in h	0·59 (0·85)	0·75 (1·11)	0·26 (0·47)	0·73 (1·41)	−0·46 (0·122)	−65·3%	0·0003
Glucose >13·3 mmol/L (240 mg/dL) within 24 h							
Time in h	1·85 (1·44)	1·91 (1·70)	1·67 (1·36)	2·06 (1·61)	−0·37 (0·163)	−19·1%	0·0247
Glucose variability							
BGRI	8·2 (2·3)	8·3 (2·7)	7·3 (2·4)	8·4 (2·6)	−0·9 (0·26)	..	0·0004
CV glucose (%)	43·0 (7·0)	42·5 (6·6)	37·6 (5·7)	41·8 (6·8)	−4·4 (0·62)	..	<0·0001
LBGI	2·7 (1·5)	2·7 (1·7)	1·8 (1·4)	2·6 (1·7)	−0·8 (0·16)	..	<0·0001
MAGE (mg/dL; average)	142 (29)	144 (31)	132 (27)	141 (31)	−8 (3·0)	..	0·0055
Mean glucose (mg/dL)	141 (19)	142 (23)	146 (20)	143 (23)	3 (2·3)	..	0·1479
Standard deviation of glucose (mg/dL)	60·6 (12·6)	60·1 (12·9)	55·0 (10·9)	59·7 (13·8)	−5·0 (1·16)	..	<0·0001
CONGA							
2 h (mg/dL)	56 (13)	56 (14)	49 (12)	58 (13)	−9 (1·3)	..	<0·0001
6 h (mg/dL)	71 (25)	69 (26)	61 (25)	72 (28)	−12 (3·4)	..	0·0004

Data in parentheses are SDs, apart from when given with adjusted means where they are SEs. AUC=area under the curve. BGRI=blood glucose risk index. CV=coefficient of variation. LBGI=low blood glucose index. MAGE=mean amplitude of glycaemic excursions. CONGA=continuous overall net glycaemic action. *Post-hoc endpoint.

***Table 2*: Glycaemic and glucose variability measures**

in the control group was consistent throughout the study, from 5·8 tests (SD 1·7) per day at baseline to 5·6 (2·2) per day at 6 months (figure 4A).

Over the study period, participants receiving multiple daily injection therapies changed their total insulin dose by a similar amount (mean −2·7 units [SD 7·3] in the

intervention group and –3·0 units [6·4] in the control group; p=0·7973). Participants receiving continuous subcutaneous insulin infusion therapy changed their total insulin dose by –0·5 units (SD 5·8) and –0·7 (3·4) units in the intervention and control groups, respectively (p=0·5860). At the end of the study there were no differences in total daily doses of insulin or bolus/basal insulin ratios between the study groups.

Patient satisfaction with treatment was significantly improved for intervention compared with control. (adjusted between-group difference –0·24 [SE 0·049]; p<0·0001). Diabetes quality of life score did not significantly favour either group in the full analysis set (–0·08 [0·039]; p=0·0524; appendix pp 14–15), but was significantly improved in the per-protocol set (appendix pp 10–13). The total treatment satisfaction (6·1 [0·84]; p<0·0001) and perceived frequency of hyperglycaemia (–1·0 [0·22]; p<0·0001) were significantly improved in the intervention group compared with the control group (figure 5). However there was no difference in diabetes distress (–0·03 [SE 0·089]; p=0·7634) or hypoglycaemia fear behaviour (0·0 [0·72]; p=0·9834) or worry scores (–1·2 [1·48]; p=0·4154; appendix pp 14–15).

276 adverse events or serious adverse events were experienced by 124 participants. There were 10 serious adverse events, five in each group, reported by nine participants. None of these were related to the device. 13 adverse events, reported by ten participants in the intervention group, were related to wearing the sensor (table 3). There were seven hypoglycaemia-related serious adverse events (requiring hospitalisation or third-party intervention) in six participants: two in the intervention group (n=2) and four in the control group (n=3). Additionally, there were three hypoglycaemia-related adverse events reported in the control group (n=2). None of the hypoglycaemic events were considered device related. There were no reported events of diabetic ketoacidosis during the study.

There were 248 sensor insertion-site signs and symptoms experienced by 65 participants across both groups. Signs can be subdivided into those expected due to sensor insertion (appendix p 17): pain (38), bleeding (25), oedema (eight), induration (five), and bruising (five), and those associated with sensor wear: erythema (85), itching (51), and rash (31). Seven participants withdrew from the study due to device-related adverse events or repetitive occurrences of sensor insertion-related symptoms.

Discussion

This randomised, controlled, multicentre, clinical trial assessed the effect of a novel glucose monitoring system on hypoglycaemia in adults with well controlled type 1 diabetes.[1] Our data show a reduced time in hypoglycaemia in the intervention group using the device compared with the control group, equating to a 38% decrease in time spent with sensor glucose lower than 3·9 mmol/L.

Notably, our trial resulted in both a decrease in time in hypoglycaemia and numerically fewer hypoglycaemic events. Previous studies of continuous glucose monitoring devices versus self-monitoring in adults with well

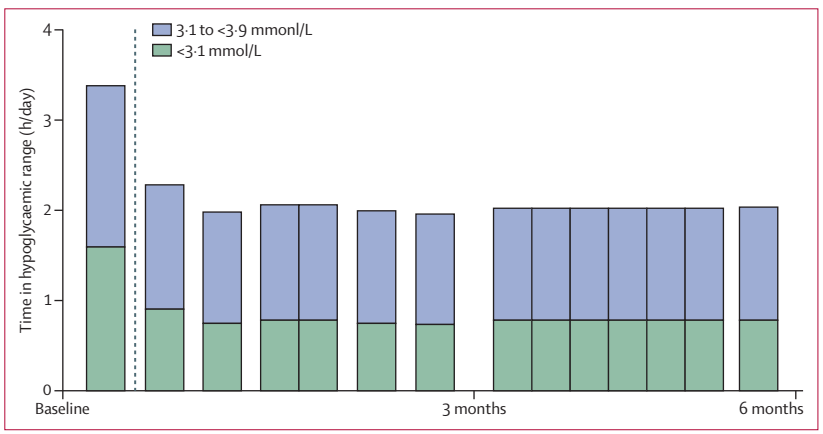

Figure 3: **Time in hypoglycaemic range during baseline and treatment phase (days 1–208) in the intervention group in the per-protocol set**
Grouped bars indicate analysis performed over 2 week periods and then averaged. Dashed line marks the start of the intervention.

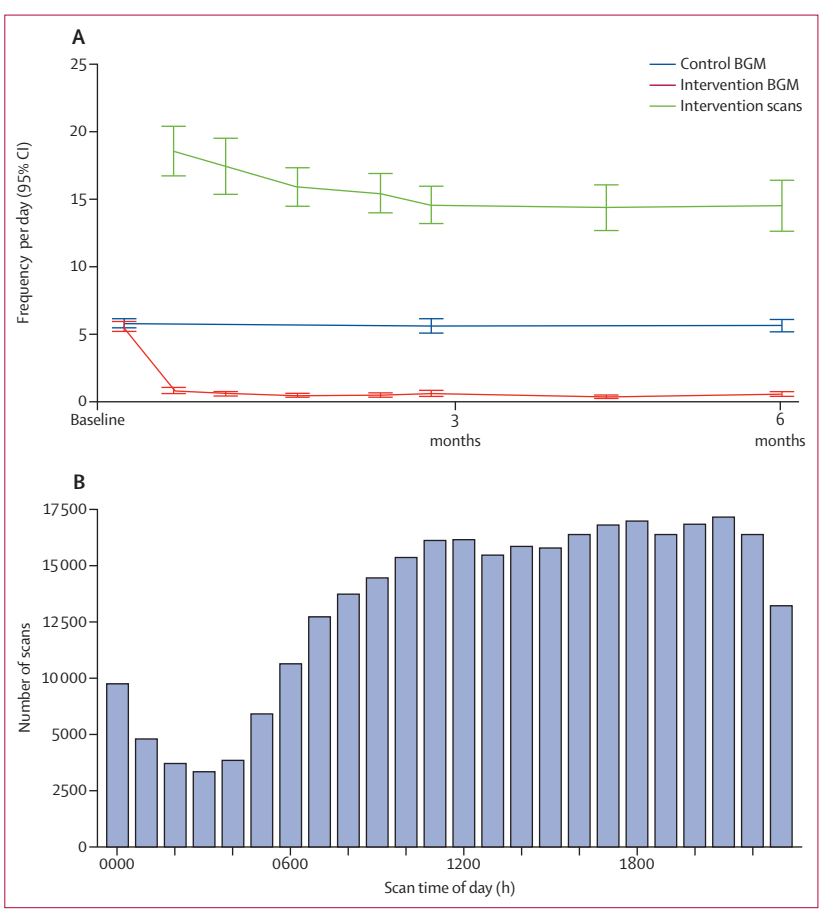

Figure 4: **Glucose monitoring frequency (A) and total number of scans by time of day in the intervention group (B)**
Number of scans performed across all intervention participants over 6 months by time of day. BGM=blood glucose monitoring.

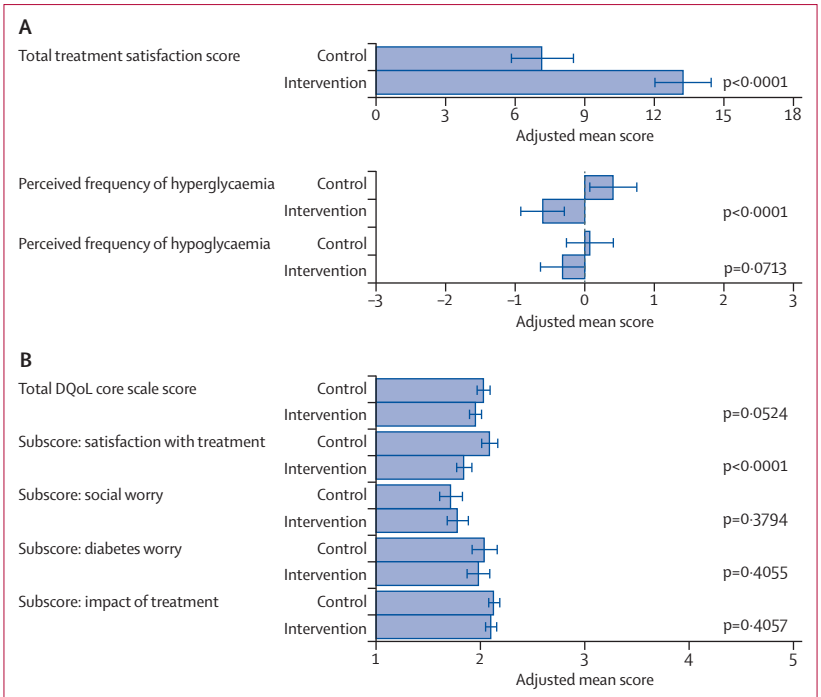

Figure 5: **Scores from DTSQ (A) and DQoL (B) questionnaires**
Data are presented for the full analysis set; for those for the per-protocol population please see appendix pp 10–13. Error bars show 95% CIs. DTSQ treatment satisfaction scores range from –18 to 18; high scores indicate much more satisfied, convenient, flexible, or likely to recommend treatment now. DTSQ perceived frequency scores range from –3 to 3; high scores indicate much more of the time now. DQoL scores range from 1 to 5; high scores indicate dissatisfaction, frequent impact, or frequent worry. DQoL=Diabetes Quality of Life Questionnaire. DTSQ=Diabetes Treatment Satisfaction Questionnaire.

	Intervention group (n=120)	Control group (n=121)
Participants with adverse or serious adverse events	63 (53%)	61 (50%)
Number of adverse or serious adverse events	138	138
Participants with serious adverse events	5 (4%)	4 (3%)
Number of serious adverse events	5	5
Participants with hypoglycaemic serious adverse events*	2 (2%)	3 (2%)
Number of hypoglycaemic serious adverse events*	2	4
Participants with hypoglycaemic adverse events	0	2 (2%)
Number of hypoglycaemic adverse events	0	3
Participants with device-related adverse events†	10 (8%)	0
Number of device-related adverse events	13	0
Participants who discontinued due to adverse events	6 (5%)	1 (<1%)‡

Table includes the full analysis set and two participants that became pregnant. *A hypoglycaemic serious adverse event was reported during the baseline phase. †Device-related adverse events were all related to wearing the sensor: four participants with allergy (one severe, three moderate); one with itching (mild); one with rash (mild); four with insertion-site symptom (severe); two with erythema (one severe, one mild); and one with oedema (moderate); all resolved. ‡Due to severe hypoglycaemia.

Table 3: **Adverse events**

controlled type 1 diabetes have only reported a decreased time spent in hypoglycaemia,[19,20] for which the presence of a low glucose alarm is expected to have had some beneficial contribution. In this study, participants with a diagnosis of severe hypoglycaemia unawareness were excluded.[7] Consequently, individuals with varying levels of hypoglycaemia awareness were included in our study (appendix p 1). Intervention participants achieved a clinically relevant reduction in hypoglycaemia and actively prevented further episodes over 6 months without depending on an alarm function or self-monitored blood glucose testing. Although we cannot delineate in detail the explanations of these consistent findings, our results might have been achieved because of the high system utilisation[21] (>90%) and scanning frequency, resulting in a three-times increase in daily self-monitoring of glucose control, which persisted throughout the 6 month study period. Time spent in hypoglycaemia was reduced almost immediately as sensor-based results became visible to participants (ie, before sensor results were reviewed with their clinician at study visits). This finding indicates fast adaptation to the device. Furthermore, it could suggest that real-time and glucose trend data, rather than retrospective analysis of the recordings, were predominantly used for proactive self-adjustments of glycaemic control. This notion is corroborated by findings showing that the effectiveness of continuous glucose monitoring depends largely on sufficient sensor utilisation[8] and that improvements in glucose control are rapidly reversed following cessation of monitoring.[10] Moreover, patient-driven use of real-time continuous glucose monitoring recordings is at least as effective as physician-led recommendations of therapy adjustments based on retrospective continuous glucose monitoring data analysis.[22] At study end, there were no differences in total daily doses of insulin or bolus/basal insulin ratios between the study groups. However, as shown previously in individuals with sensor-augmented pump therapy in whom insulin delivery was recorded in parallel with sensor glucose, day-to-day modifications of insulin administration patterns might take place without any noticeable overall changes in total insulin or relative proportion of bolus insulin.[10]

We also found that the reduction in hypoglycaemia exposure (time and events) was similar during both day-time and night-time. The pattern of daily scanning (figure 4B) shows that the highest frequency occurred in the evening, probably allowing necessary adjustments in overnight insulin supplementation or carbohydrate intake to counteract low glucose concentrations before sleep. Moreover, although scanning frequency during night-time was much lower than the day, there was still an average of one to two scans per night; together with historical data and less variable glucose in general, this might have been sufficient to reduce the incidence of nocturnal hypoglycaemia.

The observed lessening of hypoglycaemia was not at the expense of increasing the general blood glucose concentration (supported by the essentially unchanged mean sensor glucose and HbA_{1c} levels), in addition to significantly reduced time in hyperglycaemia (>13·3 mmol/L). Thus, the combination of decreases in both hyperglycaemia and hypoglycaemia resulted in an

increase in time within optimum glucose control for participants in the intervention group.

Frequency of self-monitoring of glucose was maintained by participants in the control group throughout the study period, whereas it was decreased in the intervention group and replaced with sensor scanning. This is an important indication of confidence in using current, historic, and trend sensor glucose data for self-management. Moreover, the change in behaviour in the intervention group, indicated by the negligible number of self-monitoring tests performed and high sensor scanning, might be associated with the individuals in the intervention group being able to view their glucose values more easily, rapidly, and frequently during the day or night. By comparison, self-monitoring of glucose readings provides single, intermittent measurements, which might not capture intervals of high glycaemic variability or nocturnal events that precipitate hypoglycaemia.[23] Device acceptance was further supported by the high sensor utilisation rate and the improvement in some patient-reported measures and some aspects of quality of life at 6 months. The intervention group agreed with positive aspects, including use of the system, improved treatment satisfaction, and diminished anxiety. Reduced self-monitoring of glucose[24] and hypoglycaemia[25] are factors related to subject burden that might contribute to these improvements. This concords with a recent study suggesting that perceived increased control of diabetes is associated with improved quality of life.[26] However, despite these clinically relevant reductions in hypoglycaemia, there was no change in patient-reported fear of hypoglycaemia, which supports similar findings from sensor-augmented pump therapy[10,19,27] and insulin-suspend technology studies.[11]

Several studies have shown a strong association between glucose variability and severe hypoglycaemia.[28,29] Episodes of severe hypoglycaemia in type 1 diabetes have been shown to be preceded and followed within 48 h by measurable disturbances in blood glucose.[30] Kilpatrick and colleagues[29] reported an 1·07-times increase in incidence of time to first hypoglycaemic event for every 1 mmol/L (18 mg/dL) increase in glucose standard deviation. Both glucose variability[31] and hypoglycaemia[32] are associated with inferior clinical outcomes. In this study, the use of the flash sensor-monitoring device was associated with significant improvements in several different measures of glucose variability, including a lowering of the low blood glucose index to a level compatible with low risk of severe hypoglycaemia.[32] In absolute terms, there were fewer serious adverse events and adverse events associated with hypoglycaemia in the intervention (two) than in the control group (seven). It should be noted, however, the study was not powered to detect any statistically significant differences in the incidence of adverse events associated with hypoglycaemia.

With regard to safety, adverse events relating to major sensor insertion-site events were reported by few participants. With all types of medical devices attached to the body, skin reactions are an occasional reported problem. In the present study, skin reactions occurred in 8% of participants, which we consider typical of medical-grade adhesive use.

Our trial results add to those from continuous glucose monitoring studies that have showed a reduction in hypoglycaemia alone[27] or in combination with modest improvement in HbA_{1c} levels or reduced time in hypoglycaemia without increasing HbA_{1c} levels.[11,19,20] However, there are a number of study limitations that might affect the generalisability of our findings. For individuals diagnosed with severe hypoglycaemia unawareness, this technology might not be ideal and predictive or low-threshold glucose insulin-suspend technology might be preferable.[33] Our inclusion criteria of well controlled diabetes (HbA_{1c} <7·5%) implies that participants were highly motivated and successful in their self-management compared with other populations; although a concern for this group is susceptibility to hypoglycaemia. The relative proportion of continuous insulin infusion users in the trial was higher than usually seen in most European type 1 diabetes populations,[34] and only adults were enrolled. Future studies are needed to assess the effectiveness of this novel glucose monitoring system in younger age groups in addition to less well controlled and less motivated people with type 1 diabetes. All participants experienced periods of sensor wear; consequently, the intervention was not masked to participants, investigators, and study staff. As such, treatment decisions and assessment were based on the same sensor glucose values. This is a common limitation in glucose technology studies and it is recognised that there is no practical alternative to this approach.[35] The trial took place over a period of 6 months and therefore there are limitations around expected compliance to device use over a longer period. No adjustment was made for multiple testing of secondary endpoints. Many of the endpoints, particularly those derived from sensor glucose values, are highly inter-related and should not be considered in isolation.

In summary, use of the novel flash glucose sensor system resulted in a significant reduction in time and incidence of hypoglycaemia, without deterioration in HbA_{1c} levels, demonstrating that the system is a safe replacement for self-monitoring of blood glucose and is highly acceptable to individuals with type 1 diabetes. For many individuals, hypoglycaemia is a barrier to optimum glucose control. Novel sensor-based systems to monitor glucose hold great promise as an effective alternative to conventional self-monitoring of blood glucose.

Contributors

All authors were involved in the design of the study protocol, were investigators for the study, collected data, and worked collaboratively to review and prepare the final manuscript.

Declaration of interests

JB has received honoraria for consulting or lecture fees from Abbott Diabetes Care, AstraZeneca, Insulet Corporation, Integrity Applications, and Sanofi-Aventis. RA has received consulting and speaking honoraria

from Abbot Diabetes Care. PG-D has received lecture honoraria, and serves on advisory boards for Abbott Diabetes Care, Medtronic, and Novo Nordisk. JK has received lecture honoraria from Abbott Diabetes Care, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Boehringer-Mannhein, GlaxoSmithKline, Medtronic, Merck, Sharp & Dohme, Novo Nordisk, Lilly, Roche, and Sanofi-Aventis. JK serves on advisory boards for Abbott Diabetes Care, AstraZeneca, Merck, Sharp & Dohme, Novo-Nordisk and Lilly. RW received lecture honoraria and serves on advisory boards for Abbott Diabetes Care, Allergan, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen Cilag, Medtronic, Merck, Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi, Schülke, Servier, and Takeda, and has received unrestricted study grants from Eli Lilly, Medtronic, Novo Nordisk, and Sanofi.

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Health State Utilities Associated with Glucose Monitoring Devices

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ABSTRACT

Background: Glucose monitoring is important for patients with diabetes treated with insulin. Conventional glucose monitoring requires a blood sample, typically obtained by pricking the finger. A new sensor-based system called "flash glucose monitoring" monitors glucose levels with a sensor worn on the arm, without requiring blood samples. **Objectives:** To estimate the utility difference between these two glucose monitoring approaches for use in cost-utility models. **Methods:** In time trade-off interviews, general population participants in the United Kingdom (London and Edinburgh) valued health states that were drafted and refined on the basis of literature, clinician input, and a pilot study. The health states had identical descriptions of diabetes and insulin treatment, differing only in glucose monitoring approach. **Results:** A total of 209 participants completed the interviews (51.7% women; mean age = 42.1 years). Mean utilities were 0.851 ± 0.140 for conventional monitoring and 0.882 ± 0.121 for flash monitoring (significant difference between the mean utilities; $t = 8.3$; $P < 0.0001$). Of the 209 participants, 78 (37.3%) had a higher utility for flash monitoring, 2 (1.0%) had a higher utility for conventional monitoring, and 129 (61.7%) had the same utility for both health states. **Conclusions:** The flash glucose monitoring system was associated with a significantly greater utility than the conventional monitoring system. This difference may be useful in cost-utility models comparing the value of glucose monitoring devices for patients with diabetes. This study adds to the literature on treatment process utilities, suggesting that time trade-off methods may be used to quantify preferences among medical devices.

Keywords: glucose monitoring, medical devices, time trade-off, utility.

Introduction

Health state utilities are typically used to quantify health status and quality of life in economic modeling [1]. There is a growing body of evidence suggesting that utility may be influenced not only by health status and treatment outcomes but also by the process of receiving care [2]. These *process utilities* quantify the impact of treatment process attributes such as mode of administration and dose frequency [3,4]. Although the treatment process generally has less impact on utility than on efficacy, safety, or symptom severity [5], it does matter to patients, and it could also have a direct impact on treatment adherence, which can influence outcomes [6–9]. Furthermore, small utility differences associated with treatment process could affect the results of a cost-utility analysis and therefore have important implications for subsequent decision making.

For diabetes, an important aspect of the treatment process is self-monitoring of glucose levels [10–12]. Regular evaluation of glucose levels can guide patients and health care providers when making treatment and lifestyle decisions. For example, glucose levels may be considered when calculating a safe and effective insulin dose, assessing the impact of physical activity on glucose levels, and detecting hypoglycemia [13]. Conventional glucose monitoring requires a blood sample, typically obtained by pricking the finger with a lancing device to obtain the current glucose level [14]. In contrast, the recently developed FreeStyle Libre flash glucose monitoring system (Abbott Diabetes Care, Inc., Alameda, CA) does not require routine finger pricks [15]. Instead, patients obtain glucose readings from a sensor applied to the back of the upper arm. A subcutaneous filament (which is a part of the sensor and extends outward from the bottom skin-facing part of the sensor) monitors interstitial glucose levels and stores up to 8 hours of data. Users scan the sensor with a touchscreen reader

Conflicts of interest: L. S. Matza, K. D. Stewart, and E. W. Davies are employees of Evidera, a company that received funding from Abbott for time spent conducting this study. R. Hellmund is an employee of Abbott. K. Polonsky received funding for time spent on this research. All aspects of the study design, interpretation, and decision to submit for publication were determined by the authors.

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device to see their present glucose reading and an arrow indicating the glucose level trajectory. Each sensor with its filament is worn on the arm for up to 2 weeks. After 2 weeks, patients remove the sensor and apply a new one that includes a new filament.

Differences in the process of glucose monitoring could have an impact on a patient's quality of life. If this impact were quantified in terms of health state utility, it could be useful for economic modeling. Therefore, the purpose of this study was to estimate the utilities associated with conventional and flash glucose monitoring devices. Because generic preference-based instruments such as the EuroQol five-dimensional questionnaire (EQ-5D) and utility mapping algorithms for questionnaires such as the 36-item short form health survey are unlikely to be sensitive to differences in glucose monitoring, utilities were obtained using vignette-based methods, which are well-suited for isolating the utility impact of a specific treatment process.

Methods

Health State Development

Two health state descriptions (often called vignettes or scenarios) were drafted and refined on the basis of expert clinician input, device instructions for use, and literature review. Telephone interviews were conducted with two clinicians (a UK endocrinologist [MD] and a US clinical psychologist [PhD] who specialized in diabetes) to inform health state development. Questions focused on patients' typical experiences with diabetes and glucose monitoring. Later, the clinicians reviewed multiple drafts of the health states and provided comments regarding their clarity, comprehensiveness, and accuracy.

A literature review was conducted to support the health state content, focusing on diabetes symptoms [16–20], treatment, glucose monitoring, [11,13,21–25], and the two glucose monitoring approaches represented in the health states [15,26]. Further information about the glucose monitoring devices was obtained from the instructions for use that accompanied each device [14,27].

The two health states were identical in their description of a patient with diabetes requiring insulin injections and checking glucose levels about 3 times per day (see Appendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.10.007). Published guidelines vary regarding the number of times glucose levels should be checked each day, with recommendations depending on the type of diabetes and treatment regimen [13,19,20,22,28,29]. For the current health states, a frequency of 3 times per day was selected based on consideration of the multiple guidelines and input from clinicians. Although the frequency of glucose monitoring varies among patients, 3 times per day is a common testing frequency among patients treated with multiple daily insulin injections [30].

The health states differed only by the method of glucose monitoring (conventional and flash). Therefore, any preference difference between the two health states can be attributed specifically to differences in glucose monitoring strategies. To avoid potential bias, none of the study materials named the glucose monitoring devices, and health states were not numbered or lettered. Instead, they were referred to by color (purple and blue) appearing on the border of the health state cards.

To ensure respondents understood the glucose monitoring process, each health state was presented with the corresponding glucose monitoring device, and the interviewer explained how each statement in the health states corresponded to the device parts. The device parts were presented on a device display page, which included materials necessary for 2 weeks of glucose monitoring (see Appendices B and C in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.10.007). After reviewing each health state and device display page, participants watched a brief instructional video demonstrating how each device is used.

Participants

Participants were required to be at least 18 years old, residing in the United Kingdom, able to understand study procedures, and able and willing to give informed consent. The inclusion criteria did not require that participants meet any specific clinical criteria because interviews were intended to yield utilities that may be used in cost-utility analyses for submission to health technology assessment agencies, which often prefer that utilities represent general population values [31–33]. Participants were recruited via newspaper and online advertisements.

Pilot Study

The health states were tested in a pilot study with 19 general population participants in London (10 women; mean age = 37.9 years; age range = 20–59 years). Health states were valued in time trade-off (TTO) interviews. The TTO methodology varies across studies, and the pilot study explored several variations of TTO procedures [34]. Two time horizons (10-year and a time horizon based on each respondent's self-reported life expectancy) and two trading increments (5% and 10%) were tested.

Pilot study participants consistently reported that the health states, device displays, and demonstration videos were clear and easy to understand. Some participants suggested minor revisions in formatting and word choice, and the study materials were edited accordingly. All TTO time horizons and trading intervals yielded utility scores in a similar range. The 10-year time horizon was selected for use in the subsequent main study because it was relatively easy for participants to understand and complete. In addition, this time horizon is consistent with many published studies including the commonly cited Measurement and Valuation of Health Study that derived tariffs for the EQ-5D [35,36].

Utility Interview Procedures and Scoring

After finalizing the health states and methods on the basis of the pilot study, the health states were rated in a TTO valuation study in Edinburgh and London in March 2015. All participants provided written informed consent, and the study was approved by an independent institutional review board (Ethical & Independent Review Services, Study No. 14158).

The order in which the two health states were presented was randomized (i.e., half reviewed the conventional monitoring first, and the other half reviewed the flash monitoring first). For each health state, participants reviewed the health state text and materials on the device display page, with guidance from the interviewers. During this process, interviewers introduced the health state and explained the device materials (presented on the device display page) using a standardized script. After the participants indicated that they understood the health state and device, the video was shown as a review of the device procedures.

After the participants had reviewed both health states along with the device materials and videos, they were asked which of the two they would prefer. The TTO task then began, with participants rating the health state that they were randomized to review first, followed by the second health state. Following commonly used TTO procedures [1], participants were offered a choice between spending 10 years in the health state being rated or shorter lengths of time in full health. The duration of time in full health was varied in 6-month increments in the following

order: 10 years, 0, 9.5, 0.5, 9, 1, 8.5, 1.5, 8, 2, and so on. For each health state, the utility score was calculated based on the choice in which the respondent is indifferent between *y* months or years in the health state being evaluated (i.e., 10 years) and *x* months or years in full health (followed by "dead"). The resulting utility estimate (*u*) is calculated as $u = x/y$.

After completing the TTO valuation, participants were asked to indicate their preference between the health states on a 7-point scale ranging from "strongly prefer flash glucose monitoring" (1) to "strongly prefer conventional blood glucose monitoring" (7).

Statistical Analysis Procedures

Statistical analyses were completed using SAS version 9.2 (SAS Institute, Cary, NC). Continuous variables were summarized in terms of means and SDs, and categorical variables were summarized as frequencies and percentages.

Results

Sample Characteristics

A total of 210 participants attended the interviews. One of the 210 participants was unable to complete the utility interview procedures. Therefore, the analysis sample included 209 respondents (104 from London and 105 from Edinburgh; their demographic characteristics are presented in Table 1). Nineteen participants (9.1%) reported having diabetes.

Health State Utilities and Preferences

Before the TTO valuation, most of the participants (n = 186; 89.0%) said they preferred the flash glucose monitoring health state over the conventional one. Some (n = 20; 9.6%) preferred the conventional health state, and a few (n = 3; 1.4%) had no preference.

The flash health state had a significantly higher mean utility value (0.882) than the conventional health state (0.851) (mean difference = 0.030; $P < 0.0001$) (Table 2). Of the 209 participants, 78 (37.3%) had a higher utility score for the flash health state, whereas only 2 (1.0%) had a higher score for the conventional health state. Most (n = 129; 61.7%) had the same utility score for both health states. Utilities ranged from 0.175 to 0.975 for the flash health state and from 0.125 to 0.975 for the conventional health state. A broad range of utility scores is common in TTO valuation studies, but it should be noted that most of the scores were in the upper range, and SDs were relatively small (0.121 for the flash health state and 0.140 for the conventional health state). Only 9 of the 209 respondents had a utility score of less than 0.600 for either health state.

Responses to the 7-point preference scale indicate that most participants preferred the flash glucose monitoring device (Table 1).

Table 1 – Participants' characteristics (N = 209).

Characteristic	Statistics
Age (y), mean ± SD	42.1 ± 16.2
Sex, n (%)	
Male	101 (48.3)
Female	108 (51.7)
Ethnicity, n (%)	
White	163 (78.7)
Mixed	10 (4.8)
Asian	19 (9.2)
Black	13 (6.3)
Other*	2 (1.0)
Marital status, n (%)	
Single	110 (52.6)
Married/living with partner	71 (34.0)
Other†	28 (13.4)
Employment status, n (%)	
Full-time work	79 (37.8)
Part-time work	46 (22.0)
Unemployed	14 (6.7)
Other‡	70 (33.5)
Education level, n (%)	
University degree	92 (44.0)
No university degree	117 (56.0)
Preference for glucose monitoring health states on a 7-point scale§, n (%)	
(1) Strongly prefer sensor-based	136 (65.1)
(2) Moderately prefer sensor-based	36 (17.2)
(3) Slightly prefer sensor-based	13 (6.2)
(4) Neutral with no preference between health states	4 (1.9)
(5) Slightly prefer conventional	7 (3.3)
(6) Moderately prefer conventional	8 (3.8)
(7) Strongly prefer conventional	5 (2.4)

TTO, time trade-off.

* Other ethnicities include Hispanic (n = 1) and South American (n = 1).

† Other marital status includes divorced (n = 18), separated (n = 4), widowed (n =5), and "other unspecified" (n = 1).

‡ Other employment status includes retired (n = 29), student (n = 28), homemaker/housewife (n = 6), disabled (n = 5), and carer (n = 2).

§ This 7-point scale was completed after finishing the TTO utility task.

Discussion

Most of the respondents (89%) preferred the flash glucose monitoring over the conventional one, and this preference was reflected in health state utilities. The mean difference of 0.030 between the two health state utilities is similar to previously reported differences among health states differing in treatment process attributes such as dosing strategy, treatment convenience, and screening/testing procedures [2]. Furthermore, current data indicating a preference for the flash system are consistent with positive impressions of patients who used the device in a clinical trial [15]. Overall, present findings indicate that there is a measurable difference in preference between the two glucose monitoring strategies.

Although the vignette-based method appears feasible for estimating utility associated with glucose monitoring, it should be noted that influential health technology assessment guidelines have stated a preference for utilities derived via generic measures. For example, the National Institute for Health and Care Excellence Guide to the Methods of Technology Appraisal indicates a preference for utilities derived via the EQ-5D to maximize "consistency across appraisals" [32]. This guide, however, says that utilities derived via other methods may be acceptable for economic modeling when the EQ-5D is not "appropriate." Assessment of process utilities is likely to be a situation when the EQ-5D would not be appropriate. A generic instrument designed to assess overall health status or quality of life may not be sensitive to utility differences stemming from specific treatment process attributes.

Table 2 – Health state utility scores* (N = 209).

Two diabetes health states differing only in glucose monitoring strategy, mean ± SD			t Test comparing the two health state means	
Sensor-based (flash) glucose monitoring	Conventional glucose monitoring	Difference between health states, mean ± SD	t Statistic (paired)	P value
0.882 ± 0.121	0.851 ± 0.140	0.030 ± 0.053	8.3	<0.0001

TTO, time trade-off.
* These scores were obtained via TTO interviews, and they are on a scale anchored with 0 representing dead and 1 representing full health.

A systematic review of process utilities suggests that consensus may be developing regarding methods for these studies [2]. Of the 15 studies identified in this review, only 1 used a generic preference-based measure (the six-dimensional health state short form), whereas the other 14 used vignette-based methods. An advantage of the vignette-based approach is that it can isolate the utility impact of a specific treatment process by holding all aspects of a health state constant except for the treatment process attribute.

Still, it is important to consider the limitations of the vignette method. Vignettes for the present study were drafted carefully on the basis of clinician input and published literature, whereas additional procedures ensured that participants understood the devices (i.e., device display pages, thorough standardized explanations, and videos). However, a vignette, cannot include every aspect of a patient's health and treatment, and therefore vignette-based studies are inherently limited by the accuracy and level of detail in the health state descriptions. Furthermore, comparability between vignette-based utilities and utilities derived from actual patients is not entirely clear.

One aspect of vignette construction that has been previously discussed is whether the disease should be named. In the present study, both health states named the disease (diabetes) and treatment (insulin). Some studies have suggested that naming the disease can influence the utility scores, although other studies have reported that the disease label did not affect results [37–39]. Some researchers recommend omitting the label to avoid risk of bias, whereas others prefer to include the label to ensure that the health state is clear and unambiguous. The present health states named the disease and treatment for two reasons. First, this information was necessary to provide context for glucose monitoring. Without a basic introduction to diabetes, respondents would not have understood why glucose monitoring was necessary. Second, the result of greatest interest in this study was the difference between the two health states. Even if the label would shift the scores upward or downward, this shift would have the same effect on both health state utilities, with little or no impact on the difference between utilities. Therefore, when designing this study, it was thought that the label would add clarity and context to the health states without biasing the key result.

Like many TTO studies, the interviews were conducted with a general population sample, rather than patients with the relevant medical condition. Some health technology assessment guidelines emphasize that utilities should represent the general population or societal perspective [31,32,40,41]. One advantage of using a general population sample is that results may be comparable with general population valuations of other health states in other studies, which is important if utilities from multiple sources are used in the same cost-utility model. Still, the limitations of this sampling approach must be acknowledged. First, the sampling procedures and sample size were not sufficient for the present sample to be considered nationally representative. Second, the extent to which the present general population utilities would be consistent with utilities derived from patients with diabetes is not known based on personal experience, some patients could prefer the convenience of the flash system, whereas other patients may not be interested in the flash system because they are comfortable with the conventional approach.

Overall, the present study adds to the growing body of research examining treatment process utility. Although previous studies have identified utilities associated with a range of treatment process attributes such as mode of administration and dose frequency [2], the present study is the first to quantify the utility impact associated with ongoing use of medical devices. Results provide potentially useful values that may be used to compute quality-adjusted life-years for cost-utility models focusing on treatment and management of diabetes.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.10.007 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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Background and Aims: The effectiveness of FreeStyle Libre™ Flash Glucose Monitoring System in patients with type 1 diabetes (T1DM) using MDI has not been documented. In this subgroup analysis of MDI users in the IMPACT trial, we assessed its impact on hypoglycaemia compared to conventional self-monitoring of blood glucose (SMBG).

Methods: 161 patients with well-controlled T1DM, (HbA1c 50.3 ± 6.3 mmol/mol (mean±SD) [6.76 ± 0.58%]), age 43 ± 13.1 years and duration of diabetes 21 ± 10 years) using MDI were randomised to the intervention group (FreeStyle Libre; n = 81) or to the control group (SMBG; n = 80).

Results: After 6 months, those using FreeStyle Libre significantly reduced time in hypoglycaemia (<3.9 mmol/L [70 mg/dL]) by 46.0% vs. control (mean±SE: −1.65 ± 0.283 hours per day; p < 0.0001). Time <2.2 mmol/L (40 mg/dL) was reduced by 65.6%; (p = 0.0012). The proportion of patients who achieved ≤1 hour per day in hypoglycaemia (<3.9 mmol/L) was significantly higher for those using FreeStyle Libre vs. control; 33.3% vs. 10.0%, p = 0.0005.

Time in range (3.9-10.0 mmol/L [70-180 mg/dL]) significantly improved by 0.9 ± 0.37 hours per day (mean±SE); p = 0.0106 vs. control. There was no change in HbA1c.

Using FreeStyle Libre, scanning frequency at 6 months averaged 14.7 per day, whereas SMBG tests dropped from a median of 5.4 (baseline) to 0.1 per day. In the controls, SMBG tests were 5.1 per day at 6 months.

Treatment satisfaction (DTSQ/DQoL) and perception of hypo- and hyperglycaemia (DTSQ) were significantly improved.

Conclusions: Well-controlled T1DM patients using FreeStyle Libre with MDI significantly reduced time in hypoglycaemia without deterioration of HbA1c, and reported improvements in treatment satisfaction.

033

CLINICAL UPDATE WITH A LONG TERM, UNOBTRUSIVE, FULLY-IMPLANTED CONTINUOUS GLUCOSE MONITORING SYSTEM

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Background and Aims: Recent investigational human experience with a second generation long term fully-implanted (no skin-attached elements) continuous glucose monitoring system (the GlySens® Eclipse™ ICGM® System) includes sensor implantations in five new adult human subjects, as well as same-pocket re-implantations with new sensors in six adult human subjects following completion of a 12-month initial implant period.

Methods: The Eclipse™ ICGM® system is implanted in a minor outpatient surgical procedure utilizing local anesthesia. Following sensor implantation, study subjects self-monitor blood glucose four times per day via finger stick glucose meter and undergo monthly clinic visits that include meal-based glucose excursions with YSI plasma glucose comparison measurements. Some subjects also utilize a Dexcom G4® CGM to provide additional paired values. Monthly subject interviews including a standardized survey questionnaire are conducted to assess tolerance of the device.

Results: All implantations were completed successfully and no significant sensor-adherent capsular tissue was observed during explantations. Early performance measures indicate same-pocket re-implantations may be feasible for sensor replacement/renewal.

Conclusions: Use of the fully-implanted ICGM® Sensor requires an annual user decision (whether to implant/re-implant or not) and an occasional decision to recalibrate; no body-worn components or other regular user intervention is required to receive glucose readings. This combination of features offers minimal barriers for adherence to treatment modalities requiring continuous glucose monitoring.

CAUTION - Investigational Device. Limited by United States law to investigational use. Eclipse is a trademark of GlySens Incorporated. GlySens and ICGM are trademarks of GlySens Incorporated registered in the U.S. Patent and Trademark Office.

034

EVIDENCE OF A STRONG ASSOCIATION BETWEEN FREQUENCY OF FLASH GLUCOSE MONITORING AND GLUCOSE CONTROL MEASURES DURING REAL-WORLD USAGE

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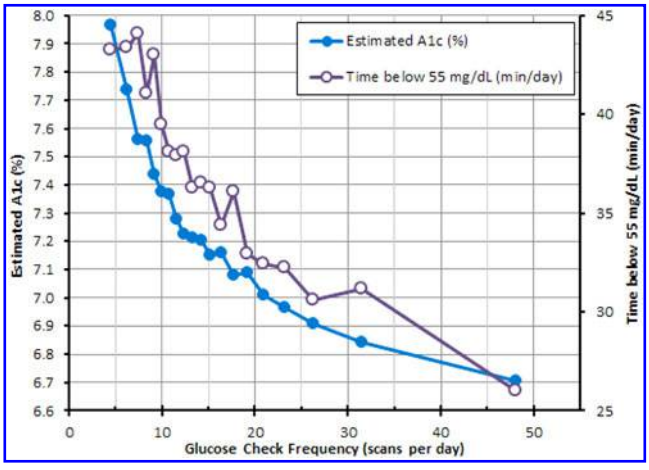
Background and Aims: The aim was to evaluate association of the real-world scanning with flash glucose monitoring (FreeStyle Libre®) and glucose control measures. FreeStyle Libre is a sensor-based glucose monitor, and the reader scans the sensor to collect the current glucose and glucose trend, along with up to 8 hours of glucose readings automatically stored every 15 minutes. When connected to the PC-based software with an active internet connection, the reader's 90-day memory is de-identified and uploaded to a database.

Methods: For analysis, sensors were required to have at least 120 hours of operation, and all sensors were grouped per reader, resulting in 50,831 readers with 279,446 sensors (86.4 million monitoring hours by 63.8 million scans). Twenty equally-sized groups by scan rate were analyzed (n = 2,542 each).

Results: Users performed an average of 16.3 scans per day (median:14, interquartile range: 10-20). Estimated HbA1c reduced (p < 0.001) as scan rate increased, from 8.0% to 6.7% from the lowest (mean 4.4 scans/day) to highest (mean 48.1 scans/day)



groups, while simultaneously time below 70, 55 and 45 mg/dL decreased by 15%, 40% and 49%, respectively (all $p < 0.001$). Time above 180 mg/dL decreased from 10.4 to 5.7 h/day (44%, $p < 0.001$), and time in range 70-180 mg/dL increased from 12.0 to 16.8 h/day (40%, $p < 0.001$).

Conclusions: In real-world use, higher rates of scanning to self-monitor glucose were found to strongly associate with improved glucose measures, including decreased mean glucose and time in hyper- and hypoglycemia as well as increased time in range.

035

EFFICACY OF CONTINUOUS GLUCOSE MONITORING IN DIABETIC PREGNANCY: THE GLUCOMOMS TRIAL

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Background and Aims: Hyperglycemia in pregnancy is associated with poor neonatal outcome. Glycemic control is traditionally monitored with self-measured glucoseprofiles and periodical HbA1c measures. We investigated the efficacy of Continuous Glucose Monitoring (CGM) in diabetic pregnancies.

Methods: In a multicenter open label randomized controlled trial, pregnant women >18 years with diabetes type 1, type 2 on insulin therapy (gestational age (GA) <16 weeks) or insulin dependent gestational diabetes (GA <30 weeks) were randomly allocated to intermittent use of retrospective CGM for 5-7 days every six weeks Glycemic control was monitored by day-curves and HbA1c checks. Macrosomia (birthweight >90th percentile), was the primary outcome. Secondary outcomes were glycemic control, maternal and neonatal complications. Primary analyses were according to intention to treat, while a secondary per-protocol analysis was limited to women using the CGM at least once every trimester.

Results: Between July 2011 and September 2015, we randomized 304 women (109 type 1, 83 type 2, 112 gestational diabetes), 150 to CGM and 154 to conventional treatment. The incidence of macrosomia was 29% in both the intervention and control group (RR .99, 95%CI .76-1.28). No difference was observed in the per protocol analysis (66% of total population, RR 1.00, 95%CI .70-1.42). Glycemic control in terms of HbA1c measures throughout pregnancy are presented in figure 1 and other outcomes in the table. Preeclampsia was less common in the CGM group, while otherwise no differences were seen on maternal and neonatal outcomes.

Conclusions: Intermittent CGM use in diabetic pregnancy does not reduce the incidence of macrosomia.

036

IMPACT OF REAL-TIME CONTINUOUS GLUCOSE MONITORING AND INTERMITTENT GLUCOSE DATA ON HYPOGLYCAEMIA FEAR IN ADULTS WITH IMPAIRED AWARENESS OF HYPOGLYCAEMIA AND TYPE 1 DIABETES

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Background and Aims: We aimed to evaluate the impact of real-time continuous glucose monitoring (RT-CGM, Dexcom G5) and intermittent flash glucose monitoring (Abbott Freestyle Libre) on diabetes-related emotional distress and fear of hypoglycaemia, using the Problem Area in Diabetes (PAID) and Hypoglycaemia Fear Survey-II (HFS-II) questionnaires respectively, in adults with type 1 diabetes (T1D) and impaired awareness of hypoglycaemia (IAH).

Methods: This is a prospective randomized parallel group study. Participants were randomized to either Libre or G5 for 8 weeks after two weeks run-in with blinded CGM. They were asked to complete the PAID (score range 0-100, higher score is worse) and HFS-II (range 0-132, higher score is worse) at baseline and endpoint.

Results: 32 adults with T1D on multiple daily injections of insulin and IAH (Gold score 4) have completed the study (66% male, mean (SD) age 50 (15) years, diabetes duration 29 (12) years, Gold score 4.7 (1), HbA1c 58 (11) mmol/mol). There was significant reduction in mean (SD) HFS-II score from baseline to endpoint with G5 (52.7(22.5) vs 47.3 (25.3), $p = 0.03$) compared to Libre (52.1(24.5) vs 50.8 (28.1), $p = 0.7$). There was no significant change in PAID score from baseline to 8 weeks with either G5 (27.9 (19) vs 27.1 (16.5), $p = 0.7$) or Libre (29.9 (20.3) vs 27.2 (20.2), $p = 0.2$). The HbA1c improved significantly in both groups.

Conclusions: Our preliminary data suggest that real-time CGM has a significantly greater benefit compared to intermittent flash glucose monitoring in reducing fear of hypoglycaemia in this high risk T1D population group.

037

HYBRID CLOSED-LOOP (HCL) THERAPY IN ADOLESCENTS AND YOUNG ADULTS WITH TYPE 1 DIABETES (T1D) INCREASES TIME IN RANGE

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Background and Aims: Changes in total daily insulin dose (TDD) and use patterns of the Medtronic HCL system in adolescents and young adults, during a 3-month outpatient trial are described.

Methods: Twelve subjects with T1D, aged 14-21 years, wore a Medtronic MiniMed™ 670G pump and Guardian™ Sensor 3 for 7 days in open loop mode, and 3 months in auto mode (HCL with manual meal boluses). Remaining in auto mode required blood glucose calibrations and avoidance of prolonged hypoglycemia

	7 days open loop	Final 7 days of 3 month auto mode period	P value
Mean Total daily insulin (units/day)	60.6 ± 16.8	63.0 ± 22.1	0.47
Mean 8am I:C ratio	7.6 ± 3.0	6.7 ± 3.0	0.02*
Mean 12 p I:C ratio	8.5 ± 3.3	7.5 ± 3.5	<0.01*
Mean 6pm I:C ratio	8.3 ± 3.3	7.0 ± 2.7	<0.01*
% in range (70-180mg/dl)	55.2 ± 15.8%	72.2 ± 10.5% while using auto mode 54.3 ± 28.9% while in open loop	<0.01* 0.91

Cost effectiveness analysis of a flash continuous glucose monitoring system for type 1 diabetes (T1DM) patients receiving intensive insulin treatment in the UK

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Background

- In patients with type 1 diabetes (T1DM), the pancreas does not secrete insulin, the hormone that stores sugars and other carbohydrates in cells. These patients must frequently measure their blood glucose level and administer insulin to alleviate symptoms of the disease.
- The FreeStyle Libre™ system, a minimally-invasive flash continuous glucose monitor ("FM") has been developed to continuously measure glucose levels from interstitial fluid using wired enzyme technology.
  - Eight hours of glucose data along with the current glucose level and trend arrow are displayed upon the reader with each scan of the sensor.
  - Each sensor may be worn for up to fourteen days and requires no calibration, thus providing glucose trends without the routine lancing and blood samples required for self-monitoring of blood glucose (SMBG).
- In intensive insulin-treated T1DM patients, the IMPACT trial (Bolinder 2016) showed that FM use reduced time spent in hypoglycaemia compared to using standard SMBG, while substantially decreasing the number of blood glucose tests.
- In addition, FM is associated with a utility improvement, as shown in a recent time tradeoff (TTO) study (Matza 2017).
- However, the relative economic value of using FM vs. SMBG in the UK setting has not yet been evaluated with evidence from the recent trial.

Objective

- To estimate the cost-effectiveness of using FM vs. SMBG using the QuintilesIMS Core Diabetes Model (QuintilesIMS CDM) for intensive insulin-treated T1DM patients in the UK.

Methods

- CDM Overview
  - The QuintilesIMS CDM, a non-product specific model (accessed via internet interface) that can be used to assess the long-term health outcomes and economic consequences for diabetes treatments, was used in this analysis. The model has been published previously in detail, and its results have been validated extensively against clinical and epidemiological studies (Palmer 2004; McEwan 2014). It has also been accepted as a valid model for use in HTA decisions (e.g. UK NICE DG 21, TA151, TA203, TA248, TA288, and TA336).
  - The IMS CDM combines Markov model structures and Monte Carlo simulation to capture major complications of diabetes and additional results including costs, life expectancy, and quality-adjusted life years (QALYs).
  - The model utilized data from the DCCT study (DCCT 1995) to estimate HbA1c progression, while other physiological parameters progressed according to data from the Framingham Heart Study (Wilson 1993).
- Analytic Overview
  - This analysis used version 9.0 of the CDM, employing bootstrapping with 1,000 simulation iterations containing 1,000 patients each over a 50-year time horizon; this approach was taken to create robust estimates and minimize Monte Carlo error.
  - The simulation estimates direct costs, life years (LYs), and QALYs over the time horizon, using a 3.5% discount rate on costs and effects, with costs reported in 2015 British Pounds (GBP).
- Model Inputs and Assumptions
  - Cohort Characteristics (**Table 1**)
    - The clinical trial population included those aged 18 years or over with well-controlled T1DM and HbA1c of ≤7.5% (58 mmol/mol) and treated by multiple daily injections of insulin or continuous subcutaneous insulin infusion for a minimum of 6 months (Bolinder 2016). Patients were testing glucose levels at least 10 times per week and were technically capable of using FM.
    - The patient characteristics in the analyses reflect the IMPACT trial population, with any inputs unavailable from the IMPACT study derived from the published literature.

Table 1: Patients Characteristics

	Value (mean)	Units
Demographics[1]		
Start age	43.7	years
Duration of Diabetes	22	years
Male	56.9%	
Racial characteristics (%)[1]		
Prop. White	99.6%	
Prop. Black	0.4%	
Prop. Hispanic or Native American or Asian/ Pacific Islander	0.0%	
Baseline risk factors		
HbA1c [1]	6.78%	
Systolic blood pressure (SBP)[1]	126.00	mmHg
Diastolic blood pressure (DBP)[1]	75.00	mmHg
Total cholesterol (T-CHOL)[1]	193.00	mg/dL
HDL[1]	72.00	mg/dL
LDL[1]	106.00	mg/dL
Triglycerides (TRIG)[1]	76.00	mg/dL
Body mass index (BMI)[1]	25.00	kg/m^2
Estimated glomerular filtration rate (eGFR)[2]	91.70	mL/min/1.73m^2
Haemoglobin[3]	14.50	g/dL
White blood cells (WBC)[3]	6.80	10^6/mL
Heart rate[4]	68.00	bpm
Waist to hip ratio (WHR)[5]	0.93	
Urinary albumin excretion rate (uAER)[6]	3.10	mg/mmol
Serum creatinine[5]	1.10	mg/dL
Serum albumin[5]	3.90	g/dL
Proportion smoker[1]	14.3%	
Cigarettes/day[1]	1.00	
Alcohol consumption[1]	1.58	oz/week

Sources: 1. IMPACT trial (Bolinder 2016); 2. Nathan 2014; 3. Hayes 2013; 4. Paterson 2007; 5. Folsom 2003; 6. Davis 2010

- Model Inputs and Assumptions
  - Treatment Effects (**Table 2**)
    - The IMPACT trial (in well-controlled patients) showed no difference in the change of HbA1c from baseline between FM and SMBG. Specifically, HbA1c increased by 0.12% from the baseline value in both arms of the IMPACT trial. It was assumed that HbA1c progressed over the time based on the DCCT study, increasing 0.045 each year (The DCCT Research Group 1995).
    - The baseline rate of symptomatic hypoglycaemic events across the two arms was applied to the SMBG arm. The sensor-based data from the trial shows that FM reduced daytime non-severe hypoglycaemia events (NSHEs) by 25.5% and nocturnal NSHEs by 33.2% compared to SMBG.
    - For severe hypoglycaemic events (SHEs), the trial results did not show any difference between the two arms; the IMPACT study was not designed to detect a difference in the rate of SHEs. Therefore, the overall number of SHEs are assumed equal for both arms, with a rate derived from published literature (UK Hypoglycaemia Study Group 2007).
  - Utility Values
    - A recent TTO study (Matza 2017) found a mean utility improvement of 0.03 associated with FM (CI 95%: 0.023-0.038) **(Table 2)**.
    - The baseline utility for T1DM was obtained from the literature (Clarke 2002) **(Table 2)**, while the remaining utility and disutility values were derived from type 2 diabetes (T2DM) publications given the lack of available inputs specific to T1DM.
    - For NSHEs, the model leveraged the Lauridsen 2014 publication to employ a diminishing disutilities approach through the built-in functionality in the model. The literature has shown that for the first few events, patients experience a higher disutility. The disutility per event decreases as patients become accustomed to experiencing NSHEs.

Table 2: Key Inputs in the Base Case

Key inputs	FM	SMBG	Source
Physiological parameters			
Change from baseline HbA1c (%-points)	0.12 (0.45)	0.12 (0.45)	IMPACT trial (Bolinder 2016)
Adverse events			
SHE2 rate (/100 patient-years)	37.76	37.76	UK Hypo Study, Foos 2015
SHE1 rate (/100 patient-years)	282.24	282.24	UK Hypo Study, Foos 2015
NSHEs rate (/100 patient-years)	4,897.10	6,760.00	IMPACT trial (Bolinder 2016)
Proportion of all events that are nocturnal	25%	27%	IMPACT trial (Bolinder 2016)
Utilities			
Annual utility score associated with treatment	0.03	0.00	Matza 2017
Baseline T1DM	0.785		Clarke 2002
Disutility for SHE2 (during daytime)	-0.055		Evans 2013
Disutility for SHE2 (nocturnal)	-0.057		Evans 2013
Disutility for SHE1 (during daytime)	-0.0183		Marrett 2011
Disutility for SHE1 (nocturnal)	-0.0183		Marrett 2011
Disutility for NSHE	Diminishing approach		Lauridsen 2014
T1DM Intervention Costs			
Annual cost (year 1)	£2,761.78	£1,775.57	Calculation
Annual cost (year 2+)	£2,709.78	£1,775.57	Calculation
Key Acute Event Costs			
SHE2	£419.56		Hammer 2009
SHE1	£0.00		Assumption
NSHE	£0.00		Assumption

- Model Inputs and Assumptions
  - Costs & Resource Utilization
    - All costs (2015 currency) are derived from national databases (medications, procedures) or the published literature (e.g. costs of complications)
    - Annual costs **(Table 2)** associated with managing T1DM were calculated according to unit prices and trial-based resource utilization, including:
      - FM Costs
        - » 26 sensors per year (1 every 2 weeks; readers are not reimbursed).
        - » IMPACT trial resource use was applied: 182.5 back-up blood glucose test strips per year, 267.4 lancets per year, 45.8 units of insulin per day, and one additional physician visit in the first year to ensure appropriate use of the device.
      - SMBG Costs
        - » IMPACT trial resource use was applied: 1,971 strips per year, 657.6 lancets per year and 38.4 units of insulin per day.
- Scenario analyses were also performed to test the robustness of base case results (**Table 3**)

Table 3: Scenario Analyses

Scenario		Description
1	Discount rate	Investigate impact of 0% discount rather than base case country-specific defaults
2	Time horizon	Explore shorter time horizons of 5 and 10 years
3	NSHE rate	Reduce the NSHE rate in SMBG arm to 29.00 events/patient year, which is derived from the UK Hypo Study (UK Hypo Study 2007). The NSHE rate in FM arm was reduced by the same percentage of daytime and nocturnal events as reported in the IMPACT trial
4	FM treatment utility	Vary treatment –related utility benefit in FM arm using the 95% CI (0.023 to 0.038)
5	Physiological parameters	Leverage trial-based physiological parameters' change rather than the assumption of 0 change
6	SMBG resource utilization - year 1	Vary the treatment cost associated with SMBG for year 1 only, given observed extra resource use from the clinical trial. Remove the cost of severe events to avoid double counting
7	SMBG resource utilization - all years	Vary treatment cost associated with SMBG for all years, given observed extra resource use from the clinical trial. Remove the cost of severe events to avoid double counting
8	SHE assumption	Assume all SHEs require medical third party assistance and use an alternative SHE disutility value from the literature (Currie 2006), reflecting categories available in the prior version of the CDM (version 8.5)
9	SHE reduction	Reduce the rate of SHEs by 55.0% for the FM arm, rather than 0% in the base case, based on a reduction in sensor-based hypoglycemic events <40 mg/dL from the clinical trial
10	SMBG use	Vary the number of test strips to explore variability in use
11	NSHE disutility	Explore variations on the disutility associated with NSHE given common input use in historical analyses

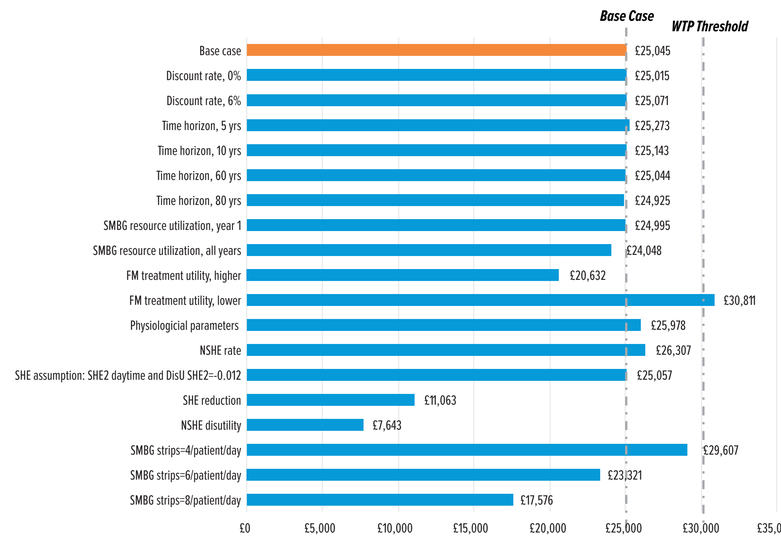
- Base case analyses (**Table 4**)
  - The base case ICER (cost/QALY) is £25,045, whereas the cost/NSHE-averted is £27.
    - Over the 50-year time horizon, FM use led to 0.73 higher QALYs due to fewer NSHEs and the utility benefit associated with FM.
    - The incremental cost of FM versus SMBG is attributed exclusively to the intervention cost in the base case.
    - As expected, there was no difference in LYs, and no differences occurred between FM arm and SMBG arm in terms of major complications, as FM and SMBG had equivalent impact on HbA1c.
    - This implies that using FM may be considered a cost-effective strategy compared to a £30,000/QALY threshold given the assumptions employed in this analysis.

Table 4: Base Case Results

	FM	SMBG	Incremental
LYs	19.10	19.10	0.00
QALYs	11.94	11.21	0.73
Direct costs	£77,971	£59,798	£18,173
Incremental cost per LY	-	-	NA
Incremental cost per QALY	-	-	£25,045

- Scenario analyses
  - Among the eleven scenario analyses performed, the highest ICER of £30,811 was associated with assuming a lower utility benefit due to the FM intervention (0.023 instead of 0.03 per year).
  - The lowest value of £7,643 was estimated when using the same static disutility for NSHEs (0.004 for daytime and 0.007 for nighttime events (Currie 2006)) as has been implemented in many past diabetes cost-effectiveness studies.

Figure 1. ICERs (base case and scenario analyses)



Discussion

- Clinical
  - The main clinical data and patient characteristics for each analysis are taken from 6-month trials, and may not exactly represent the real-world patient population or effects of FM. However, there were no trial protocol-mandated monitoring or adjustments to therapy, and therefore the results may be thought to approximate real-world use.
  - A simplifying assumption was made that glucose monitoring and insulin use do not change over time; in the absence of data, typical modelling practice is to assume that there is no difference associated with treatment; any insulin change applying to both strategies equally would not alter the conclusions of this study.
  - Given the substantial reduction in hypoglycaemia associated with the use of FM in IMPACT, it is plausible that SHEs would be reduced in real world use, due to the association found by Sreenan et al (Sreenan 2014). Hence the cost-effectiveness of FM may be understated in the base case.
- Inputs
  - In the T1DM analysis, utility estimates were derived from T2DM studies; these were used given the lack of robust utility and disutility data available for T1DM and were thus the best available option.
  - Additionally, current utility values may underrepresent the quality-of-life impact of using FM.
    - The intervention-associated utility benefit, derived from a TTO study, assumed that FM offsets the need for blood tests performed on average 3 times per day by SMBG users. However, guideline recommendations to test 6-10 times per day in T1DM may mean even greater utility benefit.
    - The disutility associated with minor (<70mg/dl) hypoglycaemic events is assumed to reflect the diminishing effect of each event as they become more frequent, as has been shown in recent research. However, this value is much smaller than that used in prior economic analyses (Currie 2006), and therefore, the ICERs in this study are likely to be very conservative relative to other published values; scenario analysis showed how favourable the analysis would become using these alternate values.
- Given these considerations, there is potential for FM to be even more cost-effective versus SMBG than the base case analysis.

Conclusion

- This analysis of FM vs SMBG shows that improved hypoglycaemia outcomes and health utility benefit of flash continuous glucose monitoring translate into economic value with incremental costs per QALY under published thresholds in the UK.
- Results were robust in scenario analysis, with only one scenario just over the UK threshold, and thus flash continuous glucose monitoring may be considered cost effective for use in T1DM patients using intensive insulin.

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Cost Calculation and Adherence to Guidelines for a Flash Continuous Glucose Monitoring System for Adults with Type 1 Diabetes Mellitus Using Intensive Insulin: a UK NHS Perspective

1325-P

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Background

- Disease management for people with type 1 diabetes mellitus (T1DM) using intensive insulin involves a balance between reducing hyperglycemia and minimizing the risk of hypoglycemia.[1]
- Barriers to achieving optimal glycemic control include the complexity of daily management, which involves frequent glucose monitoring and insulin dose adjustments, and hypoglycemia associated with insulin use.[2]
- The current standard of care is self-monitoring of blood glucose (SMBG) using blood glucose meters, lancets and test strips. The 2015 UK National Institute for Health and Care Excellence (NICE) guideline for the diagnosis and management of T1DM recommends that adults with T1DM test at least four times per day, and up to 10 times per day in certain circumstances, such as an increased frequency of hypoglycemic episodes.[3] Similarly, the 2017 American Diabetes Association (ADA) guidelines specify that patients using intensive insulin regimens should test 6–10 times (or more) daily.[4]
  - Although SMBG is widely used, many patients do not test at the required frequency owing to the inconvenience and invasiveness of the test procedure, pain and social stigma.[5,6] Inadequate adherence to SMBG monitoring guidelines is associated with poor long-term outcomes.[7]
- Healthcare spending on T1DM is rising owing to the increasing prevalence of the disease,[8] with the total annual cost of T1DM in the UK projected to rise from £1.9 billion in 2010–2011 to £4.2 billion in 2035.[9]
- The FreeStyle Libre™ system is a novel, sensor-based, factory-calibrated flash continuous glucose monitoring system that continuously measures glucose levels in a patient's interstitial fluid. Data are wirelessly transferred from the sensor (which lasts for up to 14 days) to a handheld reader.
  - In a 6-month randomized controlled trial (RCT; IMPACT) in adults with T1DM using intensive insulin therapy, flash monitoring was associated with substantial decreases in hypoglycemic events compared with SMBG.[10]
  - The scanning frequency in the IMPACT trial was high (mean of 15 tests per day) and a similar frequency was observed in a large real-world database analysis, demonstrating that flash monitoring is associated with improved adherence to guidelines for glucose testing frequency.[11]

Table 1. Base-case estimated annual monitoring costs using the flash monitoring system and SMBG (assuming routine SMBG users test 10 times per day).

		Cost (£)
Flash monitoring system		
Cost per reader		0
Cost per sensor		48.29
Cost of reader and sensor, PPPY[a]	**(A)**	1255.54
SMBG		
Cost per lancet[12]		0.04
Cost per test strip[12]		0.29
Cost of lancet and test strip		0.33
Cost for flash monitoring system users, PPPY	**(B)**	60.23[b]
Cost for routine SMBG users, PPPY	**(C)**	1204.50
Cost of flash monitoring, PPPY	**(A + B)**	**1315.77**
Additional cost of flash monitoring vs SMBG, PPPY	**(A + B – C)**	**111.27**

[a]Assumption: use of 26 sensors per year (sensor life is up to 14 days).
[b]Assumption: 0.5 SMBG tests per day, as observed in the IMPACT trial.
PPPY, per patient per year; SMBG, self-monitoring of blood glucose.

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Objective

- To estimate the costs associated with the flash monitoring system as a replacement for routine SMBG in people with T1DM using intensive insulin from a UK National Health Service (NHS) perspective.

Methods

Inputs

- Clinical inputs were based on current UK treatment guidelines, data from the IMPACT trial, real-world data from flash monitoring system users, and recent literature.
- Costs of glucose monitoring included the acquisition costs of the flash monitoring system sensors and test strips, and the costs of lancets and test strips. UK NHS costs for the year 2015–2016 were used (Table 1).[12]
- According to the product labeling, people using the flash monitoring system need to use SMBG to check readings: 1) during times of rapidly changing glucose levels; 2) in order to confirm hypoglycemia or impending hypoglycemia; and 3) if symptoms do not match the flash monitoring system reading. Based on the frequency observed in the IMPACT trial, flash monitoring system users were assumed to conduct a mean of 0.5 SMBG tests per day.

Base-case calculation: NICE guideline testing frequency

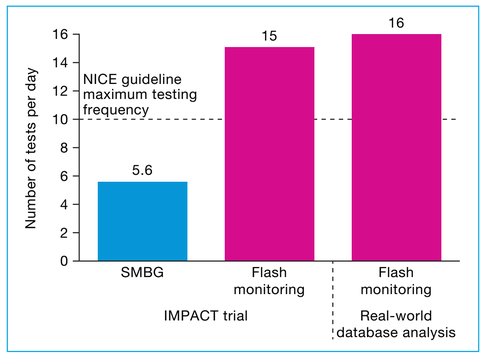
- The base-case cost calculation was created using the maximum frequency of glucose monitoring recommended by the 2015 NICE guideline (10 tests per day; Table 1).[3] NICE recommends a testing frequency of up to 10 tests per day for people with T1DM using intensive insulin who have a high frequency of hypoglycemic events (such as the participants in the IMPACT trial [Table 2], who experienced a mean of 1.30 symptomatic hypoglycemic events per week and 1.74 biochemical hypoglycemic events [glucose < 70 mg/dL] per day at baseline).
- Analysis of real-world data from over 50 000 readers has demonstrated that when given the opportunity to use the flash monitoring system, people will scan a mean of 16 times a day (Figure 1).[11] The mean SMBG testing frequency in the IMPACT trial was 5.6 times per day at the end of the study.[10] These frequencies support the use of the base-case testing frequency of 10 times per day.

Table 2. Baseline patient characteristics in the IMPACT trial.

	Flash monitoring system (n = 119)	SMBG (n = 120)
MDI (pen or syringe)/CSII (insulin pump), %	68.1/31.9	66.7/33.3
Mean age, years (SD; range)	42.4 (13.1; 18–71)	45.0 (14.6; 20–80)
Mean HbA_{1c}, % (SD; range)	6.79 (0.52; 4.4–8.0)	6.78 (0.64; 4.8–8.4)
Mean duration of diabetes, years (SD; range)	21 (10; 5–47)	23 (13; 5–59)
Mean total daily dose of insulin (SD), MDI/CSII	49.8 (23.8)/41.4 (17.1)	43.1 (19.3)/35.9 (15.6)
Mean frequency of SMBG, tests per day (SD; range)	5.4 (2.0; 3–12)	5.6 (2.3; 3–12)

CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated hemoglobin; MDI, multiple daily injections; SD, standard deviation; SMBG, self-monitoring of blood glucose.

Figure 1. Mean glucose testing frequency recommended by guidelines, and observed in the IMPACT trial and in the real-world database analysis.



NICE, National Institute for Health and Care Excellence; SMBG, self-monitoring of blood glucose.

Scenario analyses

- **Scenario 1 – RCT testing frequency:** the rate of SMBG testing observed in the IMPACT trial (5.6 tests per day) was used.
- **Scenario 2 – real-world testing frequency:** a rate of SMBG testing equivalent to the flash monitoring scan rate observed in the real world (16 tests per day) was used.

Results

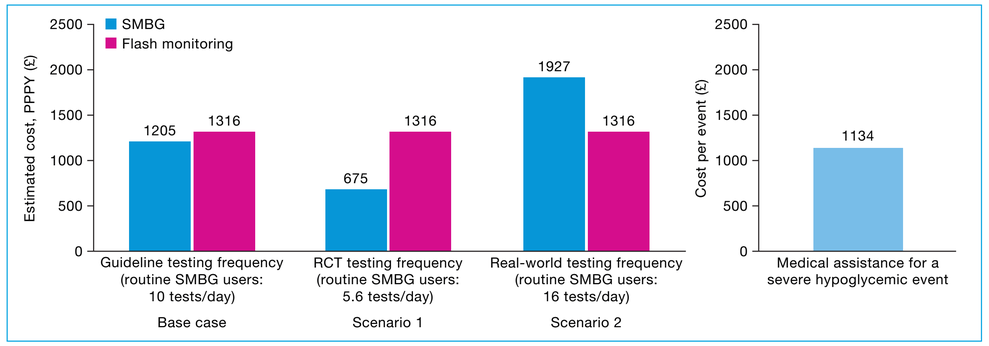
Base-case calculation: NICE guideline testing frequency

- The annual per-patient cost of glucose monitoring for routine SMBG users conducting 10 tests per day is estimated to be £1204.50. The annual cost of flash monitoring is £1315.77 (including the 0.5 SMBG tests per day observed in the IMPACT trial; Figure 2). The additional annual cost per patient using the flash monitoring system compared with routine SMBG testing is therefore estimated to be £111.27 (a 9% increase).
- This cost increment is relatively small when compared with the cost of a severe hypoglycemic event requiring hospital admission, which is approximately £1134 in 2016 prices.[13,14]
- Flash monitoring has the potential to reduce the rate of severe hypoglycemia, and so avoid some of these costs. In the IMPACT trial, flash monitoring was associated with a 48.5% reduction in low glucose events (< 45 mg/dL) compared with SMBG. Therefore, the additional cost of flash monitoring compared with SMBG in the base case may be offset by reductions in costs due to severe hypoglycemia.

Scenario analyses

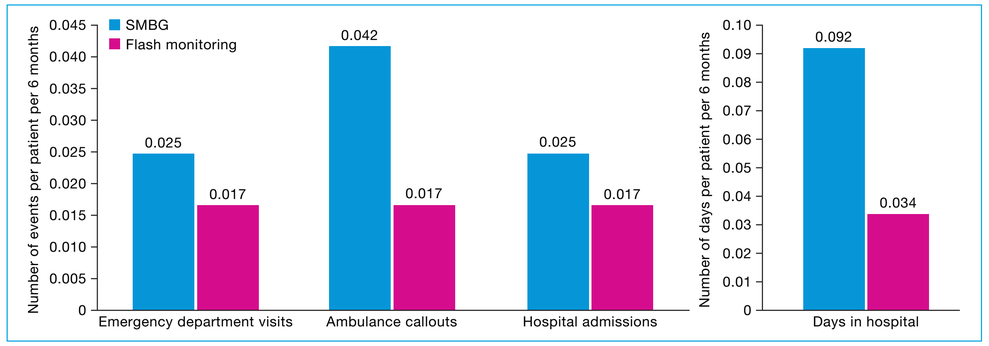
- **Scenario 1 – RCT testing frequency:** if routine SMBG users conducted 5.6 tests per day, the estimated additional annual cost of glucose monitoring for a flash monitoring user compared with a routine SMBG user would be £641.25. However, compared with SMBG at this frequency, flash monitoring provides significant clinical benefits, including reductions in hypoglycemia and hyperglycemia and increased time in the target glycemic range, as observed in the IMPACT trial.[10] In the longer term, these benefits may lead to reductions in the incidence of cardiovascular events and other complications, reducing associated costs.[15]
- **Scenario 2 – real-world testing frequency:** if routine SMBG users conducted 16 tests per day, the annual cost for flash monitoring users would be £611.43 lower than for SMBG users.

Figure 2. Costs of glucose monitoring using the flash monitoring system compared with SMBG.



PPPY, per patient per year; RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose.

Figure 3. Mean all-cause resource utilization per patient over 6 months in the IMPACT trial.



SMBG, self-monitoring of blood glucose.

Discussion

- Glucose monitoring guidelines (NICE, ADA)[3,4] suggest that people with T1DM who have frequent hypoglycemic events associated with intensive insulin use should test their glucose levels up to 10 times a day.
- The testing frequency observed in the IMPACT trial and in a large real-world database analysis demonstrate that patients given the opportunity to use the flash monitoring system choose to monitor their glucose levels at a frequency of approximately 16 tests per day.
- Flash monitoring is particularly affordable as an alternative to SMBG for people who need to conduct frequent tests to manage their high risk of hypoglycemia (e.g. people with T1DM using intensive insulin).
- At sensor prices lower than the one used in this calculation (£48.29), the flash monitoring system would be even more affordable, both for people testing very frequently and those testing less frequently than 10 times per day.
- The calculations presented here may be conservative estimates. For example, they do not include potential reductions in cardiovascular events associated with reductions in hypoglycemia[15] or potential reductions in resource use associated with flash monitoring.
  - In the IMPACT trial, reductions in all-cause resource use were observed with flash monitoring, compared with SMBG (Figure 3).

Conclusions

- Based on UK NHS costs, the flash continuous glucose monitoring system is affordable compared with SMBG in people with T1DM using intensive insulin who need to monitor their glucose levels frequently. In this population, flash monitoring is associated with changes in behavior leading to improved adherence to NICE guidelines for glucose monitoring frequency.

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Disclosures

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Richard Hellmund is a full-time employee of Abbott Diabetes Care.

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Cost effectiveness analysis of a flash continuous glucose monitoring system for type 2 diabetes (T2DM) patients receiving intensive insulin treatment in the UK

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Background

- Type 2 diabetes (T2DM) occurs when the body produces insufficient insulin for its needs. Insulin is a hormone that allows cells to store sugar and other carbohydrates as potential future energy sources for the body. As resistance to insulin grows, the body produces more insulin to compensate but eventually the body is not able to produce a sufficient amount. Initially, patients are instructed to change their lifestyle habits (e.g. exercise and diet), but patients will likely require pharmacologic treatment, including insulin therapy. When patients are on insulin therapy, they are instructed to monitor their blood glucose in order to adequately manage the disease and prevent downstream complications.
- The FreeStyle Libre™ system, a minimally-invasive flash continuous glucose monitor ("FM") has been developed to continuously measure glucose levels from interstitial fluid using wired enzyme technology.
  - Eight hours of glucose data along with the current glucose level and trend arrow are displayed upon the reader with each scan of the sensor.
  - Each sensor may be worn for up to fourteen days and requires no calibration, thus providing glucose trends without the routine lancing and blood samples required for self-monitoring of blood glucose (SMBG).
- The REPLACE trial investigated intensive insulin-treated T2DM patients and found that patients with FM had fewer hypoglycaemic events and spent less time in a hypoglycaemic state versus those using SMBG.
- Furthermore, a recently published time trade-off (TTO) study found that FM was associated with an improvement in utility (Matza 2017).
- However, the relative economic value of using FM vs. SMBG has not yet been evaluated in the UK with evidence from the recent trial.

Objective

- To estimate the cost-effectiveness of using FM vs. SMBG through the QuintilesIMS Core Diabetes Model (QuintilesIMS CDM) for intensive insulin-treated T2DM patients in the UK.

Methods

- CDM Overview
  - The QuintilesIMS CDM is a non-product specific, multiplayer internet application used to explore the long-term health and economic outcomes for diabetes treatments. Information on the QuintilesIMS CDM has been previously published in great detail, and has been extensively validated against clinical and epidemiological studies (Palmer 2004; McEwan 2014). It has also been accepted as a valid model for use in NICE decisions (e.g. UK NICE DG 21, TA151, TA203, TA248, TA288, and TA336).
  - Leveraging Markov model structures and Monte Carlo simulation, the Quintiles IMS CDM is able to capture major complications of diabetes and additional results including costs, life expectancy, and quality-adjusted life years (QALYs).
  - The model utilized the CDM default UKPDS risk equation for HbA1c value prediction for T2DM. Other physiological parameters progressed according to data from the Framingham Heart Study (Wilson 1993).
- Analytic Overview
  - This analysis used version 8.5 of the CDM, implementing a bootstrapping simulation approach over a 40 year time horizon (1,000 simulation iterations with 1,000 patients each); this allows for reliable estimates and helps to minimize Monte Carlo error.
  - The simulation estimates direct costs, life years (LYs), and QALYs over the time horizon, employing a 3.5% discount rate with results reported in 2015 British Pounds (GBP). The willingness to pay threshold considered for this analysis was £20,000 - £30,000 (NICE TA 95, TA 152, TA 166).
- Model Inputs and Assumptions
  - Cohort Characteristics (**Table 1**)
    - The REPLACE trial included patients aged 18 or older who had poorly controlled T2DM with an HbA1c of 7.5% to 12.0%. Patients were also required to be treated with either multiple daily injections of insulin or receive continuous subcutaneous insulin infusion for at least 6 months (Haak 2017). Additionally, SMBG was used at least 10 times per week and patients were required to be technically capable of using FM.
    - The patient characteristics in these analyses reflect the REPLACE trial population.
    - Values from the published literature were leveraged in the event that required inputs were unavailable from the REPLACE study.

Table 1: Patients Characteristics

	Value (mean)	Units
Demographics[1]		
Start age	59.2	years
Duration of Diabetes	17.0	years
Male	67.0%	
Racial characteristics (%)[1]		
Prop. White	96.4%	
Prop. Black	0.13%	
Prop. Hispanic	0.0%	
Prop. Native American	0.0%	
Prop. Asian/Pacific Islander	0.23%	
Baseline risk factors		
HbA1c [1]	8.68%	
Systolic blood pressure (SBP)[1]	137.00	mmHg
Total cholesterol (T-CHOL)[1]	186.00	mg/dL
HDL[1]	49.00	mg/dL
LDL[1]	99.00	mg/dL
Triglycerides (TRIG)[1]	208.00	mg/dL
Body mass index (BMI)[1]	33.2	kg/m^2
Estimated glomerular filtration rate (eGFR)[2]	77.5	$mL/min/1.73m^2$
Haemoglobin[2]	14.5	g/dL
White blood cells (WBC)[2]	6.80	10^6/mL
Heart rate[2]	72.00	bpm
Proportion smoker[1]	14.3%	
Cigarettes/day[1]	3.00	
Alcohol consumption[1]	0.87	oz/week

Sources: 1. REPLACE trial (Haak 2017); 2. Hayes 12013

- Model Inputs and Assumptions
  - Treatment Effects (**Table 2**)
    - The REPLACE trial found that there was a non-significant difference in the change in HbA1c from baseline between FM and SMBG (N=242). In the FM arm, HbA1c decreased by 0.29% from baseline while this change was 0.31% for SMBG.
    - A recent meta-analysis of T2DM patients was leveraged to establish the rate of minor hypoglycaemic events for the SMBG arm. Minor events are defined as hypoglycaemia not requiring third party assistance (Edridge 2015). The sensor data from the REPLACE trial for hypoglycaemic events under 70 mg/dl showed that after 6 months, FM was associated with a 27.7% reduction versus SMBG.
    - The REPLACE study was not powered to detect a difference in the rate of major hypoglycaemic events between the two arms and no differences were seen. In this analysis, the rate of major hypoglycaemic events was assumed to be the same in both arms, using a rate from the published literature (Edridge 2015). Major events are defined as hypoglycaemic events requiring third party assistance
  - Utility Values (**Table 2**)
    - The recently published TTO study (Matza 2017) found that FM was associated with a mean utility improvement of 0.03 (CI 95%: 0.023-0.038).
    - Utility values (both for T2DM as well as complications) were derived from the literature
    - For NSHEs, the model employed the Lauridsen 2014 publication to employ a diminishing disutilities approach by calculating the disutility per event using the NSHE rate for each arm. The literature has shown that for the first few events, patients experience a higher disutility. As patients become more accustomed to having NSHEs, the disutility per event decreases.

Table 2: Key Inputs in the Base Case

Key inputs	FM	SMBG	Source
Physiological parameters			
Change from baseline HbA1c (%-points)	-0.29 (0.78)	-0.31 (0.78)	REPLACE trial (Haak 2017)
Adverse events			
Major hypoglycaemic events (/100 patient-years)*	105.00	105.00	Edridge 2015
Minor hypoglycaemic events (/100 patient-years)*	1,685.00	2,331.00	Edridge 2015, REPLACE trial
Utilities			
Annual utility score associated with treatment	0.03	0.00	Matza 2017
Baseline T2D	0.785		Clarke 2002
Disutility for major hypoglycaemic event	-0.012		Currie 2006
Disutility for minor hypoglycaemic events	-0.0041	-0.0033	Calculated based on Lauridsen 2014
T2DM Intervention Costs			
Annual cost (year 1)	£3,964.89	£3,027.90	Calculation
Annual cost (year 2+)	£3,912.89	£3,027.90	Calculation
Key Acute Event Costs			
Minor hypoglycaemic event	£0.00		Assumption
Major hypoglycaemic event	£419.56		Hammer 2009

**"Major hypoglycaemic event" and "minor hypoglycaemic event" are the input labels used in the CDM*

- Model Inputs and Assumptions
  - Costs & Resource Utilization
    - Annual costs (Table 2) associated with managing T2DM were calculated based on UK unit prices and trial-based resource utilization, including:
      - FM Costs
        - » 26 sensors per year (1 every 2 weeks), with the assumption that readers are not reimbursed.
        - » REPLACE trial resource use was applied: 109.5 back-up blood glucose test strips per year, 251.85 lancets per year, 85.2 units of insulin per day and one additional physician visit in the first year to ensure appropriate use of the device.
      - SMBG Costs
        - » REPLACE trial resource use was applied: 1,095 strips per year, 459.9 lancets per year and 87.8 units of insulin per day.
    - Unit costs, such as medications and procedures, were obtained from national databases, while other costs, such as managing complications, were derived from the published literature.
- Scenario analyses were also performed to test the robustness of base case results (**Table 3**).

Table 3: Scenario Analyses Results

	Scenario	Description
1	Discount rate	Investigate impact of a 0% and 6% discount rather than the 3.5% default
2	Time horizon	Explore shorter time horizons of 5 and 10 years
3	FM treatment utility	Vary treatment –related utility benefit in FM arm using the 95% CI (0.023 to 0.038)
4	Resource utilization - year 1	Vary the treatment cost associated with SMBG for year 1 only, given observed extra resource use from the clinical trial. Remove the cost of severe events to avoid double counting
5	Resource utilization - all years	Vary treatment cost associated with SMBG for all years, given observed extra resource use from the clinical trial. Remove the cost of severe events to avoid double counting
6	Subgroup: <65 years of age	Utilize cohort characteristics and treatment effects matching the <65 years of age population from the REPLACE trial
7	Subgroup: 65+ years of age	Utilize cohort characteristics and treatment effects matching the 65+ years of age population from the REPLACE trial
8	Alternate minor hypoglycaemic rate and disutility	Examine the impact of the minor hypoglycaemic event rate and disutility on model results using a different rate from the published literature
9	Alternate usage of strips in SMBG arm	Vary the number of strips per day used by patients in the SMBG treatment group (4, 6, 8) as the strip use seen in the REPLACE trial is lower than what may be suitable for T2DM patients using intensive insulin

Results

- Base case analyses (**Table 4**)
  - The base case ICER (cost/QALY) is £23,842, whereas the cost/NSHE-averted is £93.
    - Over the 40-year time horizon, FM use led to higher QALYs due to fewer NSHEs and the utility benefit associated with the FM arm.
    - The incremental cost of FM versus SMBG is largely attributed to the intervention cost in the base case as the intervention cost is £12,021 higher for FM versus SMBG
    - There were negligible differences in complication rates between the two treatment arms, with 0.01 more LYs associated with the SMBG arm given the difference in HbA1c reduction (-0.31% for SMBG vs. -0.29% for FM)
    - The ICER/QALY was well below the willingness to pay threshold of £30,000/QALY

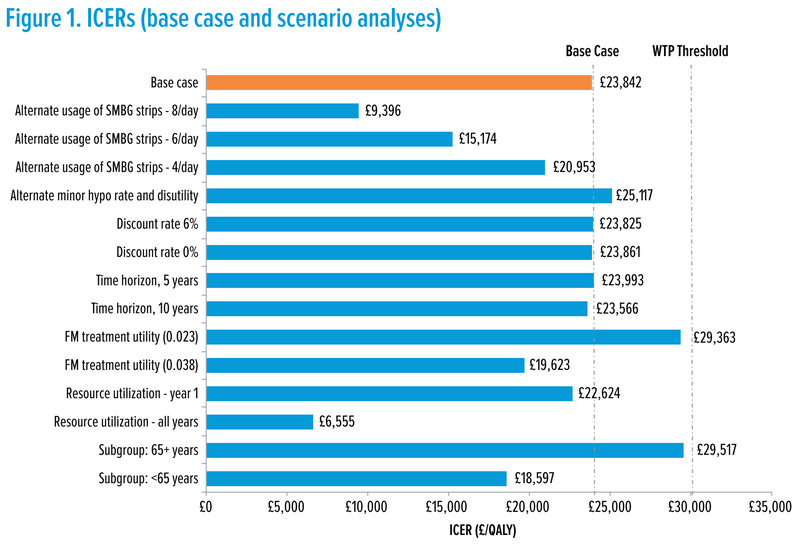
Table 4: Base Case Results

	FM	SMBG	Incremental
LYs	13.03	13.04	-0.01
QALYs	5.68	5.18	0.50
Direct costs	£88,728	£76,707	£12,021
Incremental cost per LY	-	-	NA*
Incremental cost per QALY	-	-	£23,842
Cost/minor event averted	-	-	£93

**Given the negligible incremental life expectancy, the incremental direct cost per LY is not informative*

- Scenario analyses
  - A total of 9 scenarios explored the sensitivity of inputs to model results; all scenario analyses resulted in ICERs/QALY less than the willingness to pay threshold of £30,000/QALY.
  - The scenario exploring resource use as reported in the REPLACE study, assuming it would last the duration of the model, produced the most favorable ICER/QALY of £6,555.
  - The scenario exploring the 65 and over subgroup from the REPLACE study produced the largest ICER/QALY of £29,517. This result shows that even in a subpopulation where there is no HbA1c benefit, FM remains cost-effective versus SMBG.
  - Scenario analysis results are shown in **Figure 1**.

Figure 1. ICERs (base case and scenario analyses)



Interpretation

- Clinical
  - The current analysis does not incorporate two potential facets of hypoglycaemia, including 1) the potential relationship between non-severe hypoglycaemic events and increased severe hypoglycaemic events (as was found to be true in Sreenan 2014), and 2) the potential for hypoglycaemic unawareness to increase the risk of severe events.
  - The main clinical data and patient characteristics for the analysis are taken from 6-month trials, and may not exactly represent the real-world patient population or effects of FM. However, there were no trial protocol-mandated monitoring or adjustments to therapy, and therefore the results may be thought to approximate real-world use.
- Inputs
  - Current utility values may underrepresent the quality-of-life impact of using FM.
    - The intervention-associated utility benefit, derived from a time tradeoff study, assumed that FM offsets the need for blood tests performed on average 3 times per day by SMBG users. As T2DM patients using intensive insulin require 3 or more SMBG tests per day and given that FM users in the REPLACE trial scanned a mean of 8 times per day, the utility benefit for FM could be even greater
    - The disutility associated with minor (<70mg/dl) hypoglycaemic events is assumed to reflect the diminishing effect of each event as they become more frequent, as has been shown in recent research. However, this value is much smaller than that used in prior economic analyses (Currie 2006), and therefore, the ICERs in this study are likely to be conservative relative to other published values.
- Given these considerations, there is potential for FM to be even more cost-effective than SMBG versus the analyses conducted.

Conclusion

- This analysis of FM vs SMBG shows that improved hypoglycaemia outcomes and health utility benefit due to flash continuous glucose monitoring translate into economic value with incremental costs per QALY under published thresholds in the UK.
- Results were robust in scenario analysis, and thus FM may be considered cost effective for use in T2DM patients receiving intensive insulin.

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Dear Members of the HTCC,

Thank you for accepting public comments on CGM, a revolutionary technology that has seen significant scientific advances in recent years. Although the FreeStyle Libre system was included in the assessment (Table 1, Page 20), evidence on its accuracy, clinical outcomes, and economic outcomes was not mentioned in the detailed report. On behalf of Abbott Diabetes Care, Inc., we are writing to provide scientific support of the clinical and economic effectiveness of a unique, factory-calibrated CGM device, the FreeStyle Libre system, especially given the clear evidence for hypoglycemia reduction and improved adherence to glucose monitoring in adult populations with either T1 or T2 diabetes.

The FreeStyle Libre system is the first and only FDA approved CGM device for adults with diabetes that does not require blood sample calibration and is indicated to replace blood glucose testing over 10 days of wear. It has been submitted to the Centers for Medicare and Medicaid Services for durable medical equipment coverage under the Part B Medical Benefit, satisfying all requirements as therapeutic CGM.[11]

Additional comments related to the inclusion of time in range as one of the primary intermediate outcomes, discontinuation of the FreeStyle Navigator system in the U.S., and the NICE Medtech

Innovation Briefing Report on the FreeStyle Libre system are included in Section III for consideration.

I. Clinical Evidence and Guidelines of CGM

An expert panel of physicians, researchers and individuals experienced in CGM technologies was convened at the ATTD meeting in February 2017 and tasked with developing a consensus statement on CGM use. The International Consensus on the Use of CGM was created and published in the December 2017 issue of Diabetes Care. This is the latest in a series of expert guidelines regarding the use and effectiveness of CGM[13]. The consensus classified CGM into two main categories: real-time use (rtCGM) and intermittently viewed (iCGM). Given that patients proactively use the FreeStyle Libre reader to read its sensor, the consensus committee referred to the FreeStyle Libre system as iCGM. Following review of the latest clinical evidence, the committee recommended that "CGM should be considered in conjunction with HbA1c for glycemic status assessment and therapy adjustment in all patients with type 1 diabetes and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia"[13]. The committee also recommended, "CGM data should be used to assess hypoglycemia and glucose variability" (p. 1633).

II. Clinical and Economic Evidence of the FreeStyle Libre System in Adults with Diabetes

Below is a review of the major clinical studies showing the accuracy, effectiveness and safety of the FreeStyle Libre system (FSL) in people with diabetes (PWD).

1. Accuracy

The performance of the FSL system was evaluated in a clinical study conducted at four centers with 48 participants with diabetes (95.8% Type 1, 4.2% Type 2).[26] All participants were aged 18 and older. Participants in the study required insulin to manage their diabetes. Each participant wore up to two FSL sensors on the back of the upper arm. During the study, participants tested their blood glucose using fingerstick capillary samples at least eight times during each day of the study. Participants used the blood glucose meter built into the FSL reader. Additionally, venous blood glucose was analyzed up to 128 times over four separate visits to the clinical center. Venous blood was analyzed using the Yellow Springs Instrument Life Sciences 2300 STAT Plus™ Glucose & Lactate Analyzer (YSI). YSI is a laboratory glucose and lactate analyzer of whole blood and plasma and is a widely recognized standard in laboratory analysis of blood glucose. Glucose readings obtained from the system were compared to glucose readings obtained from the YSI to evaluate the performance of the system. Three lots of sensors were evaluated in the study. Agreement between FreeStyle Libre glucose measurement and YSI reading of venous blood glucose was used to evaluate the accuracy of CGM versus YSI reference. Overall, 91.1% of results were within ±20 mg/dL / 20% of YSI reference. The overall accuracy was also measured by comparing the Mean and Median Absolute Relative Difference between the FSL and reference YSI glucose values. The Mean or Median Absolute Relative Difference gives an indication of the average percent disagreement between the CGM and the reference. Based on the 5,772-paired readings, the Mean Absolute Relative Difference was 9.7% for the comparison with YSI reference. The Median Absolute Relative Difference shows that half of the time the system was within 7.7% of the YSI reference.

Agreement between the FSL and capillary blood glucose values (BG) as measured by the reader's built-in meter was characterized by using paired FreeStyle Libre glucose measurement and BG value. Overall, 84.3% of results were within ±20 mg/dL / 20% of BG values. Based on 3,680-paired readings, the Mean Absolute Relative Difference was 12.1% for the comparison with BG value. The Median Absolute Relative Difference showed half of the time the system was within 9.4% of the BG value.

No device related serious adverse events occurred during the study. Mild skin irritations, such as erythema, edema, rash, bleeding, itching, induration, and infection were reported around the insertion site and adhesive area by a moderate frequency of participants (5 out of 48 or 10.4%). Pain was mostly reported as none, with only one instance of mild pain.

For more information regarding the accuracy of the FreeStyle Libre system, please refer to the user's manual available at https://freestyleserver.com/Payloads/IFU/2017_sep/ART38553-001_rev-C-Web.pdf

2. Efficacy and Safety

a. In Adults with T1DM

The IMPACT trial was a randomized study comparing the FSL system with the current standard of care (self-monitoring of blood glucose, SMBG) in people with T1DM[9]. Patients were enrolled from 23 European diabetes centers. The primary outcome of the study was change in time in hypoglycemia (<70 mg/dL) between baseline and 6 months. After the screening and baseline phase, 120 participants were randomly assigned to the intervention group and 121 to the control group, with outcomes being evaluated in 119 and 120, respectively. Mean time in hypoglycemia changed from 3.38 h/day at baseline to 2.03 h/day at 6 months (baseline adjusted

mean change −1.39) in the intervention group, and from 3.44 h/day to 3.27 h/day in the control group (−0.14); with the between-group difference of −1.24 (SE 0.239; $p<0.0001$), equating to a 38% reduction in time in hypoglycemia in the intervention group. The reduction in hypoglycemia exposure (time and events) was similar during both daytime and nighttime, and the pattern of daily scanning showed that the highest frequency occurred in the evening, indicating patients most likely took the necessary adjustments to their insulin or carbohydrate intake before sleep. There were also significant between-group differences favoring the intervention group compared with the control group in the glycemic variability measures. The mean number of self-monitored blood glucose tests performed per day by the intervention group immediately reduced from 5.5 (SD 2.0) tests per day in the 14-day baseline phase to 0.5 (0.7) test per day during the treatment phase of the trial. This was an unprompted response by intervention participants that clinically equates to approximately one self-monitoring blood glucose test every 2 days. The mean number of sensor scans per day for the intervention group was 15.1 (SD 6.9) during the treatment phase. Importantly, assessing patient reported outcomes showed that patient satisfaction with treatment was significantly improved for intervention compared with control (adjusted between-group difference −0.24 [SE 0.049]; $p<0.0001$). The total treatment satisfaction and perceived frequency of hyperglycemia were also significantly improved in the intervention group compared with the control group. No device-related hypoglycemia or safety issues were reported. There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device. It can be concluded from the IMPACT study that the FSL system safely reduced the time adults with well-controlled type 1 diabetes spent in

hypoglycemia, decreased glycemic variability, increased time in range and improved key patient reported outcomes.

b. In Adults with T2DM

FSL has been also studied in people with T2D[17]. In an open-label, randomized controlled study (REPLACE), adults with type 2 diabetes, on intensive insulin therapy from 26 European diabetes centers, were enrolled. Following 2 weeks of blinded sensor wear, 2:1 (intervention/control) randomization was to intervention (FSL) or control (SMBG). Primary outcome was difference in HbA1c at 6 months in the full analysis set. Prespecified secondary outcomes included time in hypoglycemia, effect of age, and patient satisfaction. Participants (n = 224) were randomized into the two groups (149 intervention, 75 controls). At 6 months, while there was no difference in the change in HbA1c between intervention and controls (-0.29 ± 0.07% [mean ± SE] and -0.31 ± 0.09%, respectively; p = 0.8222), a difference was detected in favor of FSL in participants aged <65 years (-0.53 ± 0.09% and -0.20 ± 0.12%, respectively; p = 0.0301). Time in hypoglycemia <70 mg/dL reduced by 0.47 ± 0.13 h/day (mean ± SE; p = 0.0006), and <55 mg/dL reduced by 0.22 ± 0.07 h/day (p = 0.0014) for intervention participants compared with controls, equating to reductions of 43% and 53%, respectively. SMBG frequency, similar at baseline, decreased in intervention participants from 3.8 ± 1.4 tests/day (mean ± SD) to 0.3 ± 0.7, and remained unchanged in controls (average of 3.9 ± 1.5 test/day at baseline and 3.8 ± 1.9 at the end of the study). The mean number of sensor scans per day for the intervention group was 8.3 (SD 4.4) during the treatment phase. Treatment satisfaction was higher in intervention compared with controls (DTSQ 13.1 ± 0.50 [mean ± SE] and 9.0 ± 0.72, respectively; p < 0.0001). No serious adverse events or severe hypoglycemic events were reported related to sensor data use.

In summary, the REPLACE study demonstrated that the use of FSL in type 2 diabetes treated with intensive insulin therapy resulted in no difference in HbA1c change but did reduce hypoglycemia, thus offering a safe and effective replacement for SMBG.

In a 12-month follow-up of 139 patients, enrolled in the REPLACE trial and having completed the 6-month treatment phase who continued into the open-access phase for an additional 6 months, time in hypoglycemia (sensor glucose 70 mg/dL) was reduced by 50% compared to baseline (-0.70 ± 1.85/24 h [mean ± standard deviation]; p = 0.0002) at 12 months[18]. Nocturnal hypoglycemia (2300 to 0600 hours, <70 mg/dL) was reduced by 52%; p = 0.0002. There was no change in time in range (sensor glucose 70-180 mg/dL). SMBG testing fell from a mean of 3.9 (median 3.9) times/day at baseline to 0.2 (0.0), with an average frequency of sensor scanning of 7.1 (5.7) times/day at 12 months. During this 6-month extension period, no device-related serious adverse events were reported. Nine participants reported 16 instances of device-related adverse events (e.g. infection, allergy). This follow up cohort demonstrates that the use of FSL for glycemic management in individuals with type 2 diabetes treated with intensive insulin therapy over 12 months was associated with a sustained reduction in hypoglycemia and safely and effectively replaced SMBG.

3. Real-world Evidence

De-identified data from all FSL users willing to participate were included in a real-world database. When connected to the computer-based software with an active internet connection, the FSL reader's 90-day memory was de-identified and uploaded to the database. The aim was to evaluate association of real-world scanning with the FreeStyle Libre system and glucose control measures. For analysis, sensors were required to have at least 120 hours of use. From

September 2014 to May 2016, data were collected from 50,831 readers with 279,446 sensors, comprising a total of 86.4 million monitoring hours (63.8 million scans). Twenty equally-sized groups were created based on lowest to highest rate of scanning (n = 2542 each). Six regions were identified, the five countries having the highest device use (Germany, Spain, France, UK and Italy), and a sixth "region" grouped all remaining countries. Scan rate per reader was determined and twenty equally-sized rank-ordered groups, categorized by scan frequency, were evaluated. Glucose scan frequency was analyzed together with relationship to glycemic markers in each of these regions. These analyses were reported at ATTD, ADA and EASD in 2017[1,14,15]. Real-world users of the FreeStyle Libre system scanned at a high frequency. The users performed a mean of 16.3 scans per day (median, 14; interquartile range, 10–20), with a mean of 1.6 scans per day between midnight and 6 AM. These data show that people using the FreeStyle Libre system typically monitor their glucose at a frequency that meets or exceeds that recommended by guidelines[2,24], a much higher rate than that typically achieved using SMBG. The high scanning frequency in the database is similar to the frequency observed in the IMPACT trial, demonstrating the high level of acceptance of the device by patients in a real-world setting. SMBG testing was low, with a median of 0.36 tests per day via the built-in meter, confirming the IMPACT trial finding that people did not feel the need to routinely supplement their glucose monitoring via the FreeStyle Libre system with additional SMBG.

Additionally, the higher rates of scanning were significantly associated with improved glucose control. As scan rate increased from the lowest group (mean 4.4 scans per day) to the highest (mean 48.1 scans per day), the time spent in the target glycemic range (70–180 mg/dL) increased from 12.0 to 16.8 hours per day (40% increase; $p < 0.001$), and time spent in hyperglycemia ($\geq$

180 mg/dL) decreased by 44%, from a mean (SD) of 10.5 ± 5 to 5.9 ± 5 hours per day ($p < 0.001$). The duration of time spent in hypoglycemia reduced significantly, with greater reductions seen in more severe hypoglycemic states: time below 70, 55, and 45 mg/dL decreased by 15%, 40%, and 49% respectively (all $p < 0.001$). All metrics were improved for individuals scanning at the median frequency (14 scans per day), compared with the lowest-scanning group. Estimated HbA1c in the highest scanning frequency group was significantly lower than in the group that scanned least frequently (6.7% vs 8.0%; $p < 0.001$), and there was a consistent trend towards lower estimated HbA1c as scanning frequency increased.

Average scan frequency varied significantly across regions: the highest mean scan frequency was in the UK, where participants scanned a mean of 18.0 (median, 15; IQR, 11–23) times per day and the lowest scan frequency in France, at 13.6 (median, 12; IQR, 8–17) scans per day. Participants in France spent the longest time in hypoglycemia, with a mean (± SD) of 58 (± 65) to 40 (± 62) minutes per day with glucose < 55 mg/dL in the lowest and highest frequency scanning groups, respectively. Individuals from Italy spent the least amount of time in hypoglycemia, with a mean (± SD) of 33 (± 59) to 20 (± 35) minutes per day with glucose < 55 mg/dL in the lowest and highest frequency scanning groups, respectively.

The real-world database represents an extremely large population utilizing the FreeStyle Libre system, which allows detailed assessment of measures of hyperglycemia, hypoglycemia, and self-monitoring behaviors. Limitations of the database include a lack of specific demographic data, precluding precise conclusions regarding users with type 1 or type 2 diabetes. The database also does not include data on glucose control before participants started using the FreeStyle Libre system, and conclusions about the impact of initiating system use cannot be made.

4. Cost-effectiveness Analysis

The FSL system was launched in Europe in 2014 and Canada in the summer of 2017. Following FDA approval in September 2017, the FSL system was launched in the US in November.

The assessment of cost-effectiveness of the FSL system has been based on the IQVIA Core Diabetes Model (CDM)[23]. (IQVIA were formerly known as IMS). The CDM has been used for both T1 and T2 MDI populations by pharmaceutical and medical device manufacturers, including other CGM manufacturers. CDM has been used to demonstrate the cost-effectiveness of the FSL system compared with SMBG in various European countries and Australia, based on inputs from the IMPACT and REPLACE RCTs. The T1 and T2 versions of CDM for the FSL also include a health utility increment (0.03) for the FSL compared with SMBG that was obtained from a time trade-off study [22]. This study quantified the preference of a general population for using a factory calibrated CGM, such as the FSL system to monitor glucose levels as an alternative to SMBG.

Enclosed are posters presented at ISPOR (Boston, USA 2017) demonstrating the cost-effectiveness of the FSL in T1 and T2 MDI, based on the CDM from the perspective of the UK National Health Service (NHS) [6,27]. The base case for T1 MDI shows an ICER of $33,810/QALY (GBP 25,045 assuming an exchange rate of $1.35 to a British pound) and the base case for T2 MDI shows an ICER of $32,187/QALY (GBP 23,842). These base case results were supported by various scenarios, hence it was concluded that the FSL system is cost-effective for both T1 and T2 MDI populations based on a typical UK willingness-to-pay threshold of about GBP 30,000/QALY.

The findings from the UK base case and scenarios are supported by the CDM produced for Sweden that was presented at ISPOR (Vienna, Austria 2016). These posters also included base case results from Germany, Italy, France, Netherlands, and Australia [5, 21]. These results support the conclusion that the FSL system is cost-effective across a range of health systems for both T1 and T2 MDI populations.

Additional exploratory evidence for the cost-effectiveness of the FSL system in T1 and T2 MDI from a Swedish perspective was recently presented at ISPOR (Glasgow, 2017), although this time incorporating the real-world evidence from over 50,000 readers[14]. These models show that the reductions in HbA1c and hypoglycemia that are associated with the increased frequency of glucose monitoring observed in the real world for FSL compared with SMBG support the cost-effectiveness of the FSL [7,8].

The posters for these various CDM presentations are enclosed. Manuscripts are being submitted to journals in early 2018 for publication.

There are various limitations of the cost-effectiveness models for the FSL, although these are similar to the limitations noted for the models for other CGM devices in the draft evidence report. The REPLACE and IMPACT studies were 6 months in duration, the models are not based on American healthcare inputs, and the manufacturer sponsors them. However, the ICERs provided for the FSL system for the T1 MDI population are below the lower end of the range provided by the previous studies of CGM devices. For the T2 MDI population, the ICER for the FSL system is of similar magnitude to that obtained for the T1 MDI population. Note that although this ICER for a T2 MDI population is greater than that from the only other T2 cost

effectiveness study of a CGM device in the draft evidence report, the model for the FSL was based on continuous use of the device whereas the other study was based on intermittent use. The limitations of the FSL cost-effectiveness models should also be considered alongside several reasons why the ICERs for the FSL system could be considered conservative, especially when compared with previous studies of CGM devices included in the draft evidence report:

- **Diminishing Disutility for Hypoglycemia Events compared with Fixed Disutility per Event:** Previous assessments of CGM devices[10] typically assumed a fixed disutility per non-severe hypoglycemic event (NSHE). Recent literature has shown disutility per NSHE declines with increased rates of NSHE[20], and so the average disutility per event is lower than that assumed for the earlier method [4,12]. All other things being equal, the more recent diminishing marginal disutility method as used for the FSL CDM, will tend to produce much higher ICER values than the fixed disutility method used in previous assessments. For reference, scenario 11 in Table 3 and Figure 1 of the UK NHS poster for T1 MDI shows this assumption makes a large difference to the ICER.
- **No Difference in Severe Hypoglycemia Events assumed in Base Case for FSL CDM:** The base case for the FSL CDM assumed no difference in severe hypoglycemia events (SHE) compared with SMBG, but the IMPACT and REPLACE studies showed a substantial reduction in hypoglycemic events less than 40mg/dl in favor of the FSL (55% in IMPACT, 48% in REPLACE). There is likely to be a large reduction in SHEs for the FSL that is similar to that assumed for other CGMs[10]. For example, assuming a 55% reduction in SHEs, based on events less than 40mg/dl from the IMPACT study as a proxy, the ICER for FSL in

We would also like to mention that since 2011, FreeStyle Navigator is no longer commercially available in the United States. Based on the major differences in product feature and performance between the FreeStyle Navigator and the FreeStyle Libre systems, we will leave the discretion to the reviewers whether or not the FreeStyle Navigator system should still be included in this report.

In addition to the NICE guidelines on integrated sensor-augmented pump therapy and diabetes diagnosis and management for type 1 diabetes on pages 26-28, we would like to supply the NICE Medtech Innovation Briefing on the FreeStyle Libre for Glucose Monitoring, published on July 3 2017[25]. The report recognizes the FreeStyle Libre system "as an alternative to routine blood glucose monitoring in people with type 1 and 2 diabetes who use insulin injections."

In conclusion, the use of CGM is a game-changer in the management of PWD. This revolutionary technology provides an affordable and cost-effective solution to enable PWD to gain breadth of knowledge of their glycemic measures beyond hyperglycemia, namely hypoglycemia and glycemic variability. The use of the FSL has been proven to reduce time in hypoglycemia in patients with both T1D and T2D, significantly reduce the need for SMBG and improve certain patient reported outcomes, importantly diabetes treatment satisfaction.

Sincerely,

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ORIGINAL ARTICLE

Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters

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Abstract

We review clinical instances in which A1C should not be used and reflect on the use of other glucose metrics that can be used, in substitution of or in combination with A1C and SMBG, to tailor an individualized approach that will result in better outcomes and patient empowerment.

Keywords: Glucose metrics, Glycemic biomarkers, Continuous glucose monitoring, Flash-continuous glucose monitoring.

Introduction

Frequent evaluation and precise measurement of glucose control are a crucial part of optimal diabetes mellitus (DM) care. Hemoglobin A1C (A1C), along with self-monitoring of blood glucose (SMBG), is considered the gold standard treatment target for DM, due to the intervention studies in both type 1 DM and type 2 DM, associating improved glucose control with a decreased risk of complications.[1–3] With the advent of new technologies to assess glycemia, recent evidence linking hypoglycemia with adverse outcomes, and the increased knowledge on the limitations of A1C and SMBG, new metrics need to be incorporated, to better understand the dynamic nature of glucose, how to help patients achieve optimal control, reduce complications, and also to improve patient satisfaction by decreasing the burden of the interventions recommended. Multiple parameters of glucose control other than A1C have been proposed, potentially creating a burden for DM providers.

Serum Biomarkers

Glycemic biomarkers are surrogates to estimate the risk of chronic diabetes mellitus (DM) complications. They are used to determine whether a patient's average glucose control has been maintained at target range for a determined period of time, depending on the biomarker used. There are currently four clinical biomarkers: A1C, glycated proteins: fructosamine (FA) and glycated albumin (GA), the latter not clinically available in the United States and 1, 5-anhydroglucitol (1, 5-AG).

Hemoglobin A1C

A1C, in the setting of a normal hematological profile and in the nonpregnant population, reflects mean glycemia over the previous 8–12 weeks. Its periodic monitoring is widely used and considered, along with self-monitoring of blood glucose (SMBG), the primary technique to assess DM control.[4]

Conditions that affect red blood cell (RBC) life span will impact its value, independent of glycemia.[5] The degree of such impact is currently immeasurable and frequently not fully appreciated. Table 1 summarizes common conditions that affect the accuracy of A1C and other serum glucose biomarkers.

Higher A1C values have been described in minorities, mainly African Americans (AA), across different degrees of glucose tolerance status and independent of glycemia.[6–8] Differences in the permeability of RBC to glucose, the enzymatic activity of the rate of production of A1C are some of the mechanisms proposed.[9,10] The advent of new biomarkers that do not rely on RBC survival or intracellular glucose permeability has put into question whether A1C is higher in

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Table 1. Serum Glycemic Biomarkers

Biomarker	*Strengths*	*Time represented*	*Falsely high levels*	*Falsely low levels*
Hemoglobin A1C	1. High within person reliability 2. Assay standardization in most countries 3. Requires full blood for measurement	8–12 weeks	1. Untreated iron deficiency with and without anemia [1–3] 2. Hemoglobin variants[a]	1. Hemolysis 2. Splenomegaly 3. Post-transfusion[4] 4. Drugs: erythropoietin,[5] dapsone,[6] iron[1]
Mechanism	Glycation of hemoglobin		Increased life span of RBC, decreased turnover	Decreased life span of RBC, increased turnover
Clinical utility: patients with a normal hematological profile, without conditions or medications known to affect RBC turnover.				
Glycated proteins: A. Fructosamine B. Glycated albumin	1. Not affected by alterations in RBC turnover or hemoglobin variants 2. Measured in serum, does not require full blood	2–3 weeks	1. Hypothyroidism[7] 2. Cirrhosis of the liver[8]	1. Hypoalbuminemia: protein-losing enteropathy, nephrotic syndrome, liver failure[8] 2. Hyperthyroidism[7] 3. Hyperuricemia and hypertriglyceridemia[9] 4. Nonalcoholic fatty liver disease
Mechanism	Fructosamine: glycation of serum proteins Glycated albumin: glycation of serum albumin		Increased life span of serum proteins, decreased turnover	Decreased life span of serum proteins, increased turnover
Clinical utility • Patients suffering from chronic hemolysis, abnormal RBC turnover, or hemoglobin variants known to affect A1C[a] • CKD, hemodialysis patients • Treatment phase of iron deficiency anemia • To assess early responses to treatment changes, when monthly assessments are necessary • Pregnancy complicated by diabetes				
1,5-Anhydroglucitol (1,5-AG)	1. Not affected by alterations in RBC turnover or hemoglobin variants 2. Measured in serum, does not require full blood	48 h to 2 weeks	1. CKD stage 4–5[10] 2. HNF-1 α–maturity onset diabetes of the young[11]	1. Lower levels found in nondiabetic and diabetic pregnancies[b,12] 2. Drugs: SGLT-2 inhibitors[13]

(*continued*)

Table 1. (Continued)

Biomarker	*Strengths*	*Time represented*	*Falsely high levels*	*Falsely low levels*
Mechanism	Glucose levels above the renal threshold prevents 1, 5-AG reabsorption by competition, decreasing levels in serum		Changes in the threshold of glucose in the kidney	Changes in the threshold of glucose in the kidney
Clinical utility • To detect unrecognized postprandial hyperglycemia in individuals with a hemoglobin A1C that is less than 8% • Pregnancy complicated by diabetes[b,14]				

[a]Visit http://www.ngsp.org/index.asp for more information about assay standardization and interference.

[b]Despite lower levels described in pregnancy, 1, 5-AG has shown to be a useful marker in pregnancy complicated by diabetes, see third paragraph under the section ''1,5-Anhydroglucitol''.

1,5-AG, 1,5-anhydroglucitol; CKD, chronic kidney disease; RBC, red blood cells; SGLT-2, sodium-like glucose transporter inhibitors.

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minorities independent of glycemia, suggesting such ''discrepancies'' in A1C may not always be independent of glucose.[11] Nonetheless, in clinical practice, not frequently does the etiology of such differences often remain poorly understood (case 1).

Glycated proteins

In addition to hemoglobin, other proteins can become glycated. Glycated proteins are serum proteins that have permanently changed their composition when chronically exposed to glucose and turned into irreversible ketamines. FA refers to several proteins, with albumin accounting for ~90%; GA refers exclusively to albumin.[12]

Glycated proteins have been associated with micro-[13–15] and macrovascular complications[16–21] and mortality in people with DM.[22] Several prospective studies have shown their utility for patients at risk of developing micro- and macrovascular complications.[13,23,24]

FA and GA are extracellular proteins that provide an index of average glucose over a period of 2–3 weeks, their average half-life, thus proposed as intermediate markers of glucose control. Their glycation rate is unaffected by RBC life span and therefore used in conditions in which A1C may not be a reliable marker, such as in hemodialysis patients, in whom several studies have shown superiority compared to A1C[25–27] and in whom both elevated FA and GA are risk factors for cardiovascular (CV) events, all-cause and CV mortality, independent of other confounding variables.[28] Other scenarios of their utility include the evaluation of earlier response to treatment changes or in pregnancy complicated by diabetes.[29]

As the glycation rate depends on turnover of the protein of interest, any condition affecting its half-life will in turn influence the value independent of glucose control (Table 1).

Glycated proteins present with higher values relative to plasma glucose levels in patients with liver cirrhosis, and attributed to a couple of mechanisms, (1) prolonged half-life of serum albumin originating from reduced capacities of albumin synthesis in vivo[30] and (2) increased immunoglobulin production in patients with cirrhosis,[31] (globulins tend to increase in patients with cirrhosis and hepatitis, thought to be secondary to shunting of bacterial antigens in portal venous blood away from the liver to lymphoid tissue, which induces immunoglobulin production).[32] However, as the synthetic function of the liver declines with worsening cirrhosis, albumin levels fall, and therefore in liver failure as albumin goes lower, glycated proteins will also decrease. GA is set lower in relation to plasma glucose levels in smokers,[33] hyperuricemia patients,[34] hypertriglyceridemia,[35] and men with nonalcoholic fatty liver disease (NAFLD),[36] the latter perhaps secondary to chronic microinflammation, where increase in albumin catabolism, particularly in obese subjects, shortens the half-life of albumin, decreasing glycated proteins relative to plasma glucose levels.[37]

FA concentrations are more likely to be influenced by the concentrations of protein and low-molecular-weight substances coexisting in the blood (e.g., bilirubin, uric acid),[31] while GA reflects the proportion of GA to total serum albumin, expressed by a ratio (%), as a result, the changes in serum protein concentration have less of an impact on GA than in FA.[38,39]

An important limitation to the use of glycated proteins is the lack of established clinical cut points, standardization, and data on frequency of measurements in clinical practice. Efforts have been made to estimate values similar to A1C levels,[40–45] however, clinical targets continue to be unclear.

Glucose being the main energy source has many redundant regulation mechanisms, and its clinical interpretation requires the understanding that glycemia is a dynamic process, which is a limitation true to all glycated proteins, including A1C. Glycated protein values are ''adynamic,'' making them crude measures of glycemia. Patients with similar A1C can have very different glucose patterns, rates of hypo- and hyperglycemia, and such fluctuations have an impact on A1C, depending on their severity, and unfortunately clinically unrecognizable by the value of the A1C or marker alone,[46] as such SMBG continues to be a tool to complement any of the available serum biomarkers.

The glycation gap hypothesis. The glycation of proteins is a continuous dynamic process that depends on many factors, many of them recognized (Table 1), however, others poorly understood, and perhaps not exclusively linked to average glycemia. The glycation gap (GG) refers to the difference between A1C and the A1C predicted by the serum FA. The GG is negative if measured A1C is less than A1C predicted from FA and positive if measured A1C is greater than predicted A1C. GG is zero when A1C and FA are concordant. A positive GG has been associated with the risk of microvascular complications in both type 1 and type 2 DM (T2DM).[24,47] Conversely, a negative GG has been described in patients with a lower risk of complications.[48]

1,5-Anhydroglucitol

1,5-AG is a monosaccharide, the 1-deoxy form of glucose. When glucose levels rise above the renal threshold for glucose, it will prevent 1,5-AG reabsorption, leading to its excretion and thus decreasing serum levels. 1,5-AG reflects glucose control over the previous 48 h to 2 weeks, its concentration is mainly useful in detecting postprandial glucose (PPG), where lower levels result from glucose peaks above the renal threshold and particularly useful in patients with A1C <8%.[49]

1,5-AG was found to be negatively associated with long-term risk of microvascular outcomes,[14,50,51] and an increased risk of CV disease[52–54] and mortality in DM.[53]

The concentrations of 1,5-AG decrease as pregnancy progresses in both nondiabetic and diabetic subjects[55]; nonetheless, 1,5-AG has been found to be a useful marker in pregnancy complicated by DM, associated with mean glycemia, glycemic variability (GV), and glycemic exposure in females with T1D1 in whom glycemic control was assessed by a continuous glucose monitoring (CGM) system.[56] Low levels are negatively associated with neonatal birth weight.[56–58]

The limitation of this biomarker derives mainly from renal function and factors that influence the renal threshold to glucose.[59] 1,5-AG has not been adequately studied in severe hyperglycemia and marked glycosuria (A1C >10%).[60] There are currently no guidelines of how often this biomarker should be obtained in clinical practice (Table 1).

Self-Monitoring of Blood Glucose

SMBG is a powerful tool available to patients to assess the effectiveness and safety of the regimen prescribed. For most DM patients on intensive insulin regimens, SMBG is

recommended premeals, snacks, bedtime, occasionally after eating, pre-exercise, when suspicion of and postcorrection of hypoglycemia, and pretasks such as driving.[4] Not surprisingly, there is a positive association of frequency of SMBG and improvements in glycemia.[61]

Metrics derived from SMBG

Fasting plasma glucose, PPG. The serum fasting plasma glucose (FPG) and 2-h PPG are recommended to diagnose DM.[4] The 2-h PPG seems to diagnose more people with DM as early deterioration of glucose control is characterized by loss of PPG control.[62] Both FPG and PPG provide a ''snapshot'' of glucose values, with relative contributions of these measures to A1C as A1C increases.[63,64] Numerous studies link PPG with CV disease and CV events with a plausible pathophysiology[65–68] and report that targeting PPG rather than FPG lowers CV risk,[69] although others have reported no difference in CV event rates when targeting PPG.[70] PPG is helpful to assess meal-induced glucose excursions and efficacy of DM treatment.

The glycemic risk assessment diabetes equation, average daily risk range. The glycemic risk assessment diabetes equation (GRADE) score refers to the degree of risk associated with a glucose profile. It is obtained from SMBG to quantify both hyper- and hypoglycemia by obtaining the percentage of time spent in specified given ranges (% GRADE hypoglycemia, % GRADE euglycemia, and % GRADE hyperglycemia). Values <5 correspond to euglycemia.[71]

Average daily risk range (ADRR) is computed from 1 month of SMBG data, ideally three to five readings a day. The blood glucose data need to be mathematically transformed to give appropriate weight to hyper- and hypoglycemia and converted into their corresponding risk values. They are then implemented in a spreadsheet or software and based on the distribution of the ADRR, the values are stratified into risk categories: low risk <20; moderate risk, 20–40; and high risk, >40.[72]

In patients with type 1 DM (T1DM), ADRR has shown to correlate positively with insulin sensitivity and negatively with the release of epinephrine, postulating that higher insulin sensitivity and lower epinephrine response during hypoglycemia are associated with higher GV.[73] It has been associated with A1C and negatively associated with C-peptide levels, suggesting that decreased β cell function is associated with higher GV.[74] In adults with T2DM, ADRR scores from CGM correlated with time spent below the target glucose range.[75] Several studies have found ADRR to be relatively insensitive to treatment change when using real-time CGM. ADRR appears to be a good marker/predictor of extreme glucose values but a conservative measure of GV, as summarized by Patton et al.[76]

Continuous Glucose Monitoring

Dramatic changes driven by technical advances in testing continue to take place; in turn, the results of more advanced monitoring options are increasing the evidence that the chronic complications of DM are not only the result of chronic hyperglycemia but also GV and hypoglycemia. CGM has made it apparent that periodic previous metrics are insufficient to optimally manage glycemia in DM. CGM overcomes the limitations many of the traditional metrics pose.

Several CGM systems are currently available and can be divided into retrospective, real-time, or flash-monitoring systems.

Professional retrospective CGM

Professional retrospective CGM (PCGM) refers to the use of a subcutaneous CGM that the patient wears but it is blind to the results until the provider downloads and reviews the data, with the goal of adjusting insulin doses or assessing patterns and providing education to modify patient's behaviors. In the outpatient setting, it is a tool to identify patterns and/or otherwise unrecognized reasons of poor glucose control; and in patients in whom personal CGM is not an option.

Studies have looked at PCGM utility on improving A1C, and results have been conflicting. There was no reported improvement in A1C, 7 months after the intervention in a retrospective study that included 102 patients with T1 and T2DM.[77] Others have reported an improvement on A1C in hyperglycemic patients with T1DM[78] and both T1 and T2DM,[78,79] and in patients with T2DM, having mainly hypoglycemia[78]; in this same study, there was no change in A1C in patients classified as having fluctuating glucose levels with either form of DM.[79] Durability of glucose control after PCGM revealed that the improvement at 3–5 months after PCGM was lost after 1 year.[78] An improvement in self-reported hypoglycemia has been observed.[78,79]

There are no randomized control trials or clinical guidelines on the indications for this technology. Previous retrospective studies have included hypo- and hyperglycemia,[79] in addition to GV[78] as reasons for providers to prescribe this technology to patients. Our group identified GV and hyperglycemia as the most common indications for ordering a PCGM in an academic setting, and described improvements in A1C without a significant change in frequency of SMBG or mean glucose and no difference in self-reported hypoglycemia after PCGM. Not surprisingly, in patients who performed more frequent SMBG, change in A1C was more significant.[80]

Personal CGM

In contrast with a static picture (six to eight blood glucose measurements a day), the real-time nature of this monitoring tool allows patients to intervene when glucose values change rapidly and prevent glucose excursions and exposure to hyper- and/or hypoglycemia. Personal CGM allows retrospective analysis of complete profiles, by patients at home and/or by providers in clinic or remotely, facilitating an individualized approach to DM.

Improved glycemic control, hypoglycemia rates, and patient satisfaction have been demonstrated with CGM use; despite these advantages, CGM continues to be underutilized. The cost of the device and supplies, lack of or limited insurance, and patient and provider perceptions play a role.

Clinician's lack of familiarity pose a barrier at several stages of the process: limited knowledge on candidacy for CGM, technology, software needed in clinic and time to download, interpret, and provide education and feedback to patients.

In 2013, Recommendations for Standardizing Glucose Reporting and Analysis to Optimize Clinical Decision Making in Diabetes: The Ambulatory Glucose Profile (AGP) were published; in recognizing that the widespread application of CGM was hampered by the lack of accepted measures for assessment and reporting of glucose profiles/data, likely contributing to the clinicians' reluctance to incorporate this tool in clinical practice.[81]

Metrics derived from CGM. The key metrics identified as part of the AGP were target range, glucose exposure, GV, hypoglycemia, and hyperglycemia.

Target range and time in range. Target range and time in range can be expressed either as ''% of glucose readings'' or ''hours per day.'' The proposed target range of 70–180 mg/dL was considered acceptable for clinical practice, as it has been observed that if 50% of the SMBG readings are in such range, A1C would be around 7%.[82]

Glucose exposure. Glucose exposure refers to the mean or average glucose, and a metric clinicians and patients are familiar with. Mean glucose exposure for specific time periods during CGM (e.g., overnight, fasting, 2–4 h postprandial) is helpful in evaluating the effects of food, exercise, or insulin and easy to implement in clinical practice.

Indices of GV. GV has been of interest to DM clinicians and researchers for decades. Many studies have strongly suggested that GV (the acute excursions of glucose around a mean value, that is, hyperglycemic glucose fluctuations but also hypoglycemic exposure around mean glucose) may be a significant risk factor for microvascular complications, and that it may help to explain why some patients develop microvascular complications and others having the same A1C do not.

The finding by the Diabetes Complications and Control Trial (DCCT) that patients with same A1C levels in the intensive and conventional arms of therapy had differing rates of microvascular complications[83] was a strong stimulus in the diabetes scientific community to search deeper into glycemic risk factors other than A1C as contributors of DM complications, namely GV. The subject continues to be controversial, however, it is accepted that GV is a strong predictor of hypoglycemia,[84–86] leading to poor glucose control, which in turn results in poor patient satisfaction and may increase the risk of DM burden and poor compliance. Minimizing GV is necessary to achieve glucose stability and decrease the risk of hypoglycemia.[87,88]

To standardize measures of glycemia and for the ease of use, familiarity, and correlation with other factors of glycemic control, three measures of GV were proposed: standard deviation around the mean glucose (SD), coefficient of variation (*CV*), and interquartile range (IQR).[81]

Standard deviation around the mean glucose. The metric most commonly used and understood for assessing and reporting GV is SD. SD of blood glucose was a predictor of the prevalence of peripheral neuropathy[89] and is associated with microvascular complications[90] and subclinical atherosclerosis in T1DM.[91]

Analysis of 30 measures of quality of glycemic control and variability from patients with T1 and T2DM receiving insulin during a 1-week period of using CGM concluded that most of the GV measures were highly correlated with the overall SD,[87] somewhat validating its clinical use. Criticisms to SD arise from the fact that often the glucose data are not normally distributed around the mean, and that the reliability of SD is influenced by the distribution of the data; as such, indexes with the use of formulas or equations have been developed,[72,92] however, impractical to implement in busy clinical settings.

A ratio of the mean glucose to SD has been proposed, with values of 3 considered good and values of 2 considered poor.[93] The results of Rodbard et al. were in agreement with this easy practical calculation.[87] This easy formula has become the standard in our clinic, only when the mean is between 120 and 180 mg/dL. With a ratio of 3 and the mean glucose <120 mg/dL, too much hypoglycemia is present, while with more severe mean hyperglycemia, overall control is obviously poor.[87]

Coefficient of variation. Derived from SD ($100 \times$ SD/mean of observations). The relative constancy of its percentiles irrespective of A1C or mean glucose levels, preventing a strong dependency of SD and other measures of mean glucose values, characterizes *CV* as a good parameter of GV. A good metric for research purposes, however, not easily displayed and therefore less helpful as part of the CGM clinical view.

If there is a low mean glucose and a large SD and hence a large *%CV*, the risk of hypoglycemia will be high. In contrast, if both the mean and SD are high but with a low *%CV*, the risk of hypoglycemia will be relatively low. Similarly for the risk of hyperglycemia, a high mean will generate a high frequency of hyperglycemia that is relatively insensitive to the magnitude of the SD. A lower mean could generate a high risk of hyperglycemia if the SD is large but not if the SD were small.

The correlation of *%CV* with risk of hypoglycemia has been observed,[85] enhancing its utility as a GV parameter.[94] It is hopeful that *%CV*, which has become the standard for measurement of GV in clinical research, will become available for clinical use in the future.

Interquartile range. IQR takes the difference between the 75th and 25th percentiles of glucose values, and that 50% of glucose values are the IQR. It has the advantage of being easily recognized and not dependent on the assumption of normal distribution. It allows easy visibility of the time of day or relationship to a meal or medication that there is high GV, which may need clinical attention.[95,96]

Hypoglycemia. Hypoglycemia is the major barrier in patients with DM and the limiting factor to achieve euglycemia.[97] Studies have linked hypoglycemia with excessive morbidity and mortality.[98–100] In light of the importance of reduction of hypoglycemia, efforts have been made for a consensus on reporting its frequency and severity.[101] Consensus from the AGP to report hypoglycemia in users of CGM categorized it corresponding to glucose levels: low if glucose is <70 mg/dL; very low if <60 mg/dL, and dangerously low if <50 mg/dL. The percentage of glucose values below these thresholds and time in each range, as well as number of episodes (defined as at least 10 consecutive min below the criteria) of each range, were also recommended to

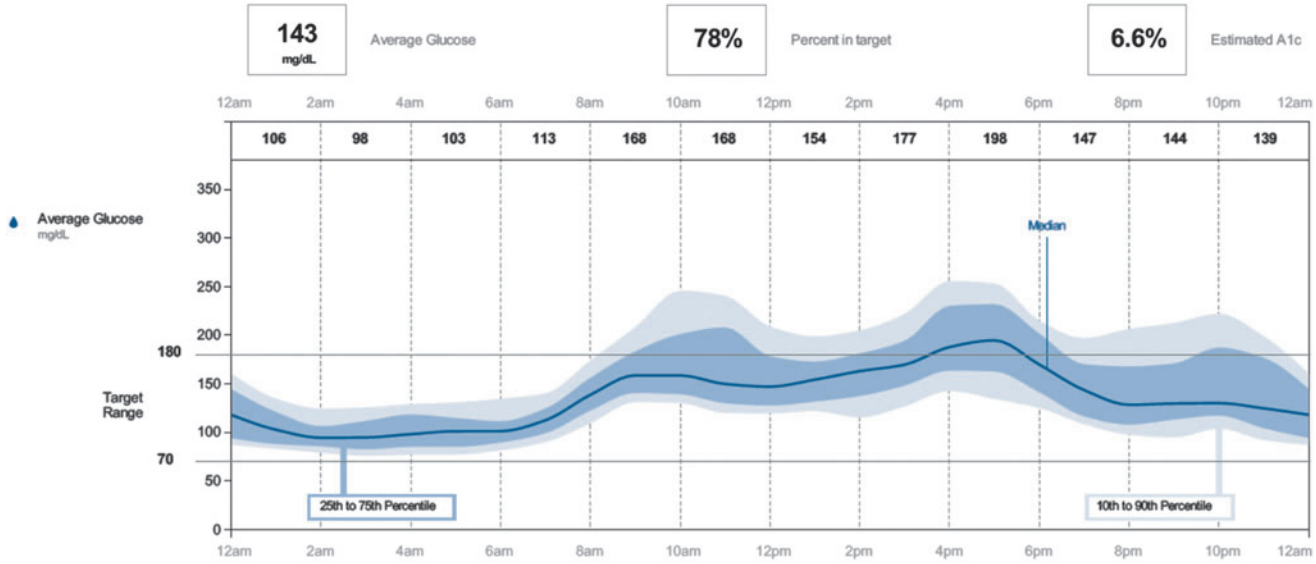

FIG. 1. FCGM in a 60-year-old African American woman with a falsely elevated A1C of 8.1%.

be reported. A Joint Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes proposed the following glucose levels when reporting hypoglycemia in clinical trials: level 1: glucose alert value of 70 mg/dL or less; level 2: a glucose level <54 mg/dL, a sufficiently low value to indicate serious, clinically important hypoglycemia, and level 3: severe cognitive impairment requiring external assistance for recovery.[4,102]

Hyperglycemia. Levels of severity above the upper range of the target of 180 mg/dL for glucose are recommended as follows: high >180 mg/dL; very high >250 mg/dL, and dangerously high >400 mg/dL. As with hypoglycemia, a clinically based category of severe hyperglycemia, that is, diabetic ketoacidosis, was recommended to advance surveillance from the patient's part and the clinical team (i.e., troubleshooting technical issues with pump therapy, hydration, and more frequent insulin correction) to prevent escalation of ketonemia and hospitalizations.

Flash Glucose-Sensing Technology

The flash continuous glucose monitoring (FCGM) system technology is a factory-calibrated interstitial glucose monitoring system, currently available as a professional, blind to the patient option (FreeStyle® Libre™ Pro), and also as a personal monitoring system intended to substitute SMBG. FCGM uses a wired glucose oxidase enzyme coimmobilized on an electrochemical sensor, worn on the back of the arm for up to 14 days. The personal FCGM is currently not available in the United States. Patients obtain a real-time reading on demand as often as every minute by scanning the sensor with a reader. Data are transferred from the sensor to the reader memory and stored automatically every 15 min allowing to show trends for the previous 8 h on the screen, rate, and direction of glucose. The FCGM has no alarms. The data can be uploaded to obtain summary reports, for personal review or in clinic by DM providers.

FCGM is accurate, with reported overall mean absolute relative difference (MARD) of 11.4% for sensor results and stable over 14 days of use when compared with capillary BG reference values, and unaffected by body mass index, age, type of DM, clinical site, insulin administration, or A1C.[103] The use of FCGM has been associated with improvement in glucose control in both uncontrolled T2 and T1DM, and maintained for up to 24 weeks of using the device.[104] In well-controlled patients with T1DM, the use of FCGM reduced the time spent in hypoglycemia by 38% at 6 months (intervention group) versus controls (SMBG).[105] The benefits in reduction of hypoglycemia by the use of FCGM have subsequently been reproduced in patients with both T1 and T2DM on treatment with insulin. In younger than 65-year-old T2DM patients, FCGM decreases A1C, while also reducing time in hypoglycemia by 43%, 53%, and 64% in ranges of <70 mg/dL, <55 mg/dL, and <45 mg/dL, respectively, when compared to the SMBG group. Nocturnal and daytime hypoglycemia decreased by 54% and 31%, respectively. Interestingly in this study, of the 224 randomized participants, in those aged >65 years, FCGM did not decrease A1C, compared to the control group (SMBG), nonetheless, time in hypoglycemia was reduced by 56% in FCGM users.[106]

A direct head-to-head comparison of CGM (Dexcom G4 Platinum) and FCGM showed that glucose profiles and MARD in outpatients with T1DM for up to 14 days were similar between the two sensors and no significant difference was detected in the estimation of clinical diagnostic parameters.[107] FCGM has been positively associated with treatment satisfaction and measures of quality of life.[105,106,108]

Figure 1 gives a good example on how FCGM can impact DM therapy. In a 60-year-old AA woman with T2DM on metformin and sulfonylurea, A1C was 8.1% and testing 2×/day her mean glucose was 132 mg/dL. This was suspicious for an inaccurate higher than predicted by SMBG A1C. FCGM showed a mean of 143 mg/dL and an estimated A1C of 6.6%. This degree of difference is not uncommon in AA, the FCGM confirmed the discrepancy between her glucose and her A1C.

Conclusions

A1C continues to be the gold standard for assessing glucose control in patients with DM, however, it has become evident that in clinical practice, many instances exist where A1C will not be a true reflection of average glucose, because its accuracy has been compromised by a variable affecting RBC survival and/or because of a GG. At the present time, all currently available glycemic biomarkers have advantages and limitations and it remains unclear which marker or combination of them may have the best relationship to complications for different populations of patients. For an individual patient, all of our biomarkers, including A1C, give a crude evaluation of glucose control.

Clinicians managing patients with DM should become familiar with a more expanded definition of optimal glucose control that includes not only A1C (when accurate) but also a combination of other metrics that reflect more realistically the dynamic nature of glucose control, by taking into consideration the period examined, limitations of each metric selected, comorbidities, medications (insulin, oral hypoglycemic), and also the feasibility and burden of the intervention recommended (SMBG, CGM, FCGM).

Recognizing the interplay between glucose control and behavior in DM, personal CGM and FCGM arise as an option to document and to intervene in the prevention of many components within the dysglycemia frame, not only reflected by average glucose or A1C but also by fluctuations and their potential short- and long-term risks. Personal CGM is now another option for many patients to better document if there indeed is a GG, and even if not, how more informative decisions can be made. CGM reported in a standardized way has the potential to help clinicians empower patients and decrease the burden of living with DM and its complications.

Author Disclosure Statement

Dr. Lorena Alarcon-Casas Wright has no conflicts of interest. Dr. Irl B. Hirsch is a consultant for Abbott Diabetes Care, Intarcia, Roche, and Valeritas.

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[redacted]

From: [redacted]
Sent: Friday, December 8, 2017 5:43 PM
To: HCA ST Health Tech Assessment Prog
Subject: PLEASE READ Dexcom continuous blood monitoring system

To Whom it may concern:

I KNOW THIS IS LENGTHY BUT PLEASE, PLEASE READ.

I am a 31-year-old female who was diagnosed with Type I diabetes about 11 months ago. The diagnosis has been life changing for me. I have had a difficult time with controlling my blood sugars. I seem to fluctuate up and down easily and I don't always have the ability to poke my finger and check my BG as often as is necessary to check where I am at with these significant BG level swings. I have been told through diabetes education that I will learn to "feel" when I am going high or low. Unfortunately I "feel" better at 250-300 and I "feel" low when I am at 175. I have anxiety problems and the fear of going low makes me very anxious. I have experienced too many times my BG going as low as 20 and I have drank two juice boxes, candy, peanut butter and jelly sandwich + more and it took over one hour to get BG level to 50 and over another hour to get over 100. This is very difficult to negotiate when it happens at work. Molina approved paying for blood glucose monitoring system and Dexcom sent me the device and then when it was time to put an order in for new supplies I was told that Molina would no longer cover this blood glucose monitoring system. I have used the continuous blood monitoring system for two weeks and it has been helping me to understand my diabetes better because I am able to see my BG levels every 5 minutes and I can get alarms before my sugars get high or begin to go lower. The fear and anxiety I have had has decreased greatly. THIS DEVICE MAKES ME FEEL HOPEFUL IN THAT I WILL BE MORE SUCCESSFUL DEALING WITH THIS LIFE LONG, SERIOUS, INCURABLE DISEASE AND THE RESULTS OF COMPLICATIONS OF DIABETES LIKE HEART DISEASE, EYE SIGHT, KIDNEY ISSUES, CIRCULATION, NUMBNESS ETC.
I do not understand why Medicaid would not want to pay for something that would help with preventing or at least diminish the complications that come with having diabetes. Diabetes will dictate every aspect of my life, every single day for the rest of my life.

If I cannot convince you with the above comments that the continuous blood monitoring system can help me 24 hours a day to negotiate the diabetes and the complications of diabetes then maybe I can appeal to your sensibilities that covering the continuous blood glucose monitoring system would be advantageous to Molina and financially prudent to Molina. In the last 11 months I have been hospitalized at least 3 x with DKA and about 2 x going to ER and received DKA protocol treatment and was able to be released without being admitted. I have lost 60 pounds in 11 months and I am now 115 pounds. I really cannot lose too much more weight. This is directly attributed to poor blood sugar control.

I know the continuous blood sugar monitoring system is not a "miracle" device. But I am convinced that using this device will be an important part in helping my success with understanding my diabetes. The device gives me the ability I to make small adjustments with my blood glucose levels vs going high and then try to make big insulin adjustments only to go too low and then having to adjust with food and so the cycle goes. With being able to see my BG level every 5 minutes I am confident that in 6 months my AC 1 numbers will improve.

Please consider covering this device. It gives me hope and some peace that this device is my helper.

Sincerely,
[redacted]