Washington State Health Care Authority

Continuous glucose monitoring – update

Final evidence report

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Continuous Glucose Monitoring

– Update –

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Abbreviations

AE: adverse event
AUC area under the curve
CGM: continuous glucose monitoring
CI: confidence interval
DM diabetes mellitus
F/U: follow-up
HbA1c: hemoglobin A1c
HR: hazards ratio
HR-QoL: Health-Related Quality of Life
IQR: inter-quartile range
JDRF: Juvenile Diabetes Research Foundation trial
MD: mean difference
NC: not calculable
NR: not reported
NS: not statistically significant
OR odds ratio
QoL: quality of life
RCT: randomized controlled trial
RD: risk difference
RoB: risk of bias
RR: risk ratio
SD: standard deviation
SF-36: Short Form-36
SMBG: self-monitoring of blood glucose
SMD: standardized mean difference
WMD: weighted mean difference

Executive Summary

Introduction

Diabetes mellitus (DM), or diabetes, is a serious metabolic disease characterized by chronic elevation of blood glucose (i.e., hyperglycemia) resulting from defects in insulin secretion, insulin action, or both. No definitive cure is known at this time. Diabetes is categorized into three major types based on etiology: Type 1 diabetes (T1DM) (formerly called juvenile diabetes or insulin-dependent diabetes mellitus [IDDM]), Type 2 diabetes (T2DM) (formerly called adult onset diabetes mellitus [AODM] or non-insulin dependent diabetes [NIDDM]), and gestational diabetes mellitus (GDM).

Diabetes is a leading cause of morbidity and mortality and is associated with substantial healthcare and societal costs. An estimated 29.9 million Americans (9.3% of the population) had diabetes in 2015 and, by 2050, the prevalence of diabetes in the U.S. adult population is projected to increase to between 21% and 33%.[12] T2DM is the most common form and accounts for 90% to 95% of all diabetes. Serious complications related to diabetes include diabetic ketoacidosis (DKA), which occurs when fatty acids called ketones build-up in the bloodstream, and hyperosmolar hyperglycemic nonketotic syndrome (HHNS) characterized by extremely high blood glucose levels without the presence of ketones, as well as longer term morbidity due to microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., heart disease, stroke) complications; other diabetes related complications include increased risk of infections, cancer and other autoimmune disorders including celiac sprue, thyroid disease, rheumatoid arthritis, and vitiligo.

For T2DM, oral, non-insulin mediations are generally used initially in combination with lifestyle management education to attain glycemic control. Not all those with T2DM will require insulin. Insulin therapy is the only effective therapy for persons with T1DM and is used for T2DM who cannot produce sufficient insulin[2,10] and pregnant women with any type with elevated glucose.[42] The insulin dose depends on body weight, age, food intake, and activity. Intensive insulin therapy, a term used to describe tight management of blood glucose levels, has been shown to reduce the risk of long-term diabetic complications by lowering average blood sugar levels, but also increases the risk of hypoglycemia, which can result in serious morbidity and even death, and causes fear of hypoglycemia which is a major barrier to optimal glucose control. Insulin may be delivered via multiple daily injections or via continuous subcutaneous insulin infusion using an insulin pump. Greater fluctuation in blood glucose levels may be seen in patients requiring insulin and more attention to monitoring blood glucose levels may be needed.

Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) are two techniques that persons with diabetes can use at home to help them maintain blood glucose within a safe range. Real-time continuous glucose monitoring (CGM) is advanced glucose monitoring technology that continuously measures interstitial glucose levels via subcutaneously placed sensor. Real-time CGM displays the current blood glucose level as well as the direction and rate of change, allows for evaluation of glycemic variability and uses alarms and alerts to inform patients when blood glucose is exceeding or falling below specified thresholds.[13] Conventional fingerstick self-monitoring of blood glucose (SMBG), sometimes called intermittent monitoring, is a technique for testing blood glucose using a portable glucose meter designed for home use. SMBG provides an instantaneous reading of current blood glucose levels at single points in time, but cannot indicate whether the glucose level is on its way up or

down. CGMs were designed to aid in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long term therapy adjustments, which may minimize these excursions.

CGM devices initially received FDA approval to be adjunctive, acting to complement rather than replace SMBG for treatment decisions and therapy modifications and required that sensors be calibrated using SMBG based on concerns that inaccuracies would lead to inappropriate treatment decisions. Technological advances resulting in improved accuracy and usability of CGM devices have led to recent approval of devices for therapeutic (versus adjunctive) use i.e., as a *replacement* for fingerstick BG testing for diabetes treatment decisions. Within the past year, several devices (T:slim X2 Insulin Pump with Dexcom G5 Mobile CGM system, the Dexcom G5 Mobile CGM System alone, and the Freestyle Libre Flash CGM System) have been FDA approved for non-adjunctive use, allowing them to replace SMBG in making treatment decisions. The MiniMed 670G System has an automatic mode during which the device administers basal insulin at rates based on the glucose values from the CGM device. Apart from the FreeStyle Libre Flash CGM system, which is factory calibrated, SMBG tests are needed to calibrate CGM devices. While the Libre Flash CGM is included as a CGM device there are important differences between it and other approved devices in the technology and how it is used which are described in the full report. Briefly, traditional CGM devices consist of a subcutaneously placed sensor connected to a transmitter that relays information via radiofrequency to a monitoring and display device and provides alerts when thresholds for high or low glucose values are sensed. Unlike traditional CGM, a transmitter is not worn and no passive glucose information is available to the user with the flash CGM. The sensor must be actively scanned with a special reader to obtain glucose measurements, trends and messages related to high or low glucose values. If a patient does not scan the flash glucose monitor, there is no indication or alert of glucose values that are too high or too low. For purposes of this report, devices will be distinguished as traditional CGM and flash CGM.

CGM devices can be used as stand-alone devices or in conjunction with compatible insulin pumps. When CGM is used together with an insulin pump, it may be referred to as sensor augmented pump therapy (SAP).

Policy Context

This topic was originally reviewed in 2011. It is proposed for re-review based on new evidence and newly expanded indications for continuous glucose monitoring (CGM). New evidence and indications are identified that support re-reviewing the evidence for continuous glucose monitoring.

Objectives

The first aim of this report is to update the 2011 HTA on glucose monitoring in children and adolescents by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of continuous glucose monitoring in persons under 18 years old with insulin requiring diabetes mellitus. The second aim is to systematically review, critically appraise and analyze research evidence on the safety and efficacy continuous glucose monitoring in persons with type 1 or type 2 diabetes (regardless of insulin requirement), including pregnant women with pre-existing or gestational diabetes. SMBG as a stand-alone means of monitoring blood glucose will not be included as an intervention. This report does not include evaluation of insulin delivery systems (automated or other).

Key Questions

In persons with diabetes mellitus (DM):

1. What is the evidence of efficacy and effectiveness of continuous monitoring?
2. What is the evidence of the safety of continuous glucose monitoring?
3. What is the evidence that glucose monitoring has differential efficacy or safety issues in subpopulations?
4. What is the evidence of cost-effectiveness of continuous glucose monitoring?

Inclusion and exclusion criteria are summarized as follows and are detailed in the full report. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Persons with diabetes mellitus, including those with type 1 and type 2, and pregnant women with pre-existing diabetes or gestational diabetes
- **Interventions:** FDA-approved real-time continuous glucose monitoring devices and FDA-approved combination devices integrating real-time continuous glucose monitoring with insulin pump/infusion (including sensor augmented insulin pumps)
- **Comparators:** Self-monitoring using convention blood glucose meters, attention control, blinded or sham CGM and usual care. Comparisons of one CGM device with another with another will be excluded
- **Outcomes:** Primary clinical outcomes are 1) microvascular complications, 2) macrovascular complications, 3) fetal outcomes, cesarean section rates. Primary intermediate outcomes are 1) achieving target (i.e. age-appropriate) HgA1C level, 2) maintaining target (i.e. age-appropriate) HgA1C level, 3) acute episodes of hypoglycemia. Safety outcomes are 1) mortality, 2) morbidity from glucose meters or monitors. Economic outcomes are cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcomes.
- **Studies:** Focus is on high quality comparative studies (e.g. randomized trials) for Key Questions 1-3; observational studies with long term clinical outcomes or safety will also be considered for Key Questions 1-3. Full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be sought for Key Question 4; studies using modeling may be used to determine cost-effectiveness over the full duration of glucose monitoring, which is a lifetime.

Methods

The scope of this report and final key questions were refined based on input from clinical experts and public comments received on draft key questions. Clinical expert input was sought to confirm critical outcomes on which to focus.

A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed to identify relevant peer reviewed literature as well as other sources (National Guideline Clearinghouse, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments. Our 2011 report served as a basis for updating information on people ≤18 years old requiring insulin and a 2012 AHRQ report served as a base source of RCTs for other populations[22] and is summarized in the report background.

Studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature.

Included studies were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. The SoE for was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[1] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[9] The strength of evidence was based on the highest quality evidence available for a given outcome. Briefly, bodies of evidence consisting of RCTs were initially considered as High strength of evidence. The strength of evidence could be downgraded based on the limitations (i.e., risk of bias, consistency of effect, directness of outcome, precision of effect estimate, and reporting/publication bias). When assessing the SoE for studies performing subgroup analysis, we also considered whether the subgroup analysis was preplanned (*a priori*) and whether a test for homogeneity or interaction was done. There are also situations where nonrandomized studies could be upgraded if large magnitude of effect (strength of association) or a dose-response relationship is observed if all known confounders were adjusted for and there was no downgrade for any of the domains. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

• High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.

• Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.

• Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.

• Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

We summarized evidence separately for Type 1 and Type 2 diabetes and diabetes during pregnancy (gestational and preexisting type 1 or 2); results were further stratified by age (children, adults, or mixed children and adults) within each category. The intervention of interest was real-time continuous glucose

monitoring, referred to in this report simply as CGM. Retrospective use of CGM devices was an excluded intervention.

We conducted meta-analyses when there were two or more studies with similar indications, interventions, control groups and outcomes. Most of the included trials reported data at 3, 6 and 12 months.

Two general types of randomized controlled trials were considered for this review: the more traditional parallel design and cross-over trials. In parallel RCTs, patients are randomly allocated to specific groups and remain in those groups throughout the duration of the trial. In cross-over trials, patients receive different treatments at different time periods. Cross-over trials offer some benefits when used appropriately, however, this design is subject to unique sources of bias and statistical methods which account for repeated measures on the same patients and other design features are required. Meta-analysis across cross-over trials and with parallel trials is generally problematic and more fully described in the Cochrane Handbook and other publications. For this HTA, data from parallel and cross-over trials are reported separately. There is currently no standardized, validated methodology for formal critical appraisal of cross-over trials.

Results

Number of studies for each comparison of efficacy for included conditions.

Overall, 28 randomized trials (in 35 publications)[4-8,11,17-19,23,25-27,31,33,34,36-38,40,43-47,50,52,54,56,58-62,64] that reported efficacy and safety outcomes were included. Additionally, 14 observational studies met inclusion criteria,[3,14,16,21,24,29,30,32,35,39,48,51,53,63] six of which were follow-up studies or open-label phases of included RCTs (4 of the JDRF trial).[14,16,29,30,32,35] The selection of the studies is summarized in the table below. Additionally, five economic studies were included.[15,20,28,41,49] Please note that some publications may have included secondary outcomes only and may not be represented in this executive summary but are in the full report. Observational studies are described in the full report.

Diabetes and age categories*	Number of studies	Included studies	Industry funded?
TYPE 1 DM			
Children	5 RCTs (8 publications)[8,26,33,34,36,40,50,54]	*In previous report:* 3 RCTs (4 publications)	
		Bergenstal 2010 (STAR 3, index trial)*	**Yes**
		Hirsch 2008*	**Yes**
		JDRF 2008 (index trial)*	No
		Lawrence 2010 (JDRF f/u study)*	No
		New to report update: 2 RCTs (4 publications)	
		Mauras 2012	No
		Slover 2012 (STAR 3, f/u study)	**Yes**
		Rubin 2012 (STAR 3, f/u study)	**Yes**
		Kordonouri 2010 (ONSET, index trial)	**Yes**

Diabetes and age categories*	Number of studies	Included studies	Industry funded?
	9 observational[14,29,32,35,39,48,51,57,63]	*In previous report:* 3 studies	
		Chase 2010 (JRDF f/u study)	No
		JDRF 2010 (f/u study)*	No
		JDRF 2009[a] (f/u study)*	No
		New to report update: 6 studies	
		Rachmiel 2015	No
		Wong 2014	No
		Kordonouri 2012 (ONSET, f/u study)	**Yes**
		Ludwig-Seibold 2012	**Yes**
		Scaramuzza 2011	No
		Tansey 2011 (JDRF f/u study)	No
Adults	12 RCTs (15 publications)[6,8,11,25,26,33,34,37,38,43,45,46,50,59,60]	Beck 2017[a] (DIAMOND, index trial)	**Yes**
		Polonsky 2017 (DIAMOND, f/u study)	**Yes**
		Lind 2017 (GOLD, index trial)†	**Yes**
		Bolinder 2016 (IMPACT, index trial)‡	**Yes**
		van Beers 2016 (IN CONTROL, index trial)†	**Yes**
		New 2015	**Yes**
		Tumminia 2015†	**Yes**
		Langeland 2012†	No
		Hermanides 2011	**Yes**
		Bergenstal 2010 (STAR 3, index trial)*	**Yes**
		Rubin 2012 (STAR 3, f/u study)	**Yes**
		Peyrot 2009	**Yes**
		Hirsch 2008*	**Yes**
		JDRF 2008 (index trial)*	No
		Lawrence 2010 (JDRF, f/u study)*	No
	8 observational[3,29,30,32,39,55,57,63]	Soupal 2016	No
		Wong 2014	No
		Ludwig-Seibold 2012	**Yes**
		Anderson 2011	**Yes**
		Tansey 2011 (JDRF f/u study)	No
		JDRF 2010 (f/u study)*	No
		JDRF 2009[a] (f/u study)*	No
		JDRF 2009[b] (f/u study)	No

Diabetes and age categories*	Number of studies	Included studies	Industry funded?
Mixed (children and adults)	8 RCTs (9 publications)[4,5,17,26,27,31,33,34,44,47]	Battelino 2012 (SWITCH, index trial)†	**Yes**
		Hommel 2014 (SWITCH, f/u study)†	**Yes**
		Battelino 2011	**Yes**
		JDRF 2009 (index trial)*	No
		O'Connell 2009	**Yes**
		Raccah 2009	**Yes**
		Hirsch 2008*	**Yes**
		JDRF 2008 (index trial)*	No
		Lawrence 2010 (JDRF, f/u study)*	No
		Deiss 2006	**Yes**
	2 observational[29,32]	JDRF 2010 (f/u study)*	No
		JDRF 2009[a] (f/u study)*	No
TYPE 2 DM			
Adults	5 RCTs (7 publications)[7,18,23,56,58,61,64]	Beck 2017[b] (DIAMOND, index trial)	**Yes**
		Haak 2016 (REPLACE, index trial)‡	**Yes**
		Tildesley 2013 (index trial)	No
		Tang 2014 (f/u to Tildesley 2013)	No
		Ehrhardt 2011 (index trial)	**Yes**
		Vigersky 2012 (f/u to Ehrhardt 2011)	**Yes**
		Yoo 2008	**Yes**
	1 observational[24]	Haak 2017 (REPLACE, f/u study)‡	**Yes**
DM WITH PREGNANCY (Preexisting Type 1 and 2, and Gestational)			
Type 1 DM	2 RCTs[19,52]	Feig 2017	**Yes**
		Secher 2013	**Yes**
	3 observational[16,21,53]	Secher 2014	No
		Cordua 2013 (f/u to Secher 2013)	**Yes**
		Fresa 2013	Unclear
Type 2 DM	1 RCT[52]	Secher 2013	**Yes**
Gestational	1 RCT[62]	Wei 2016	Unclear

DM: diabetes mellitus; f/u: follow-up; RCT: randomized controlled trial
*Some trials contributed data to more than one category; to the extent possible we reported data separately for children, adults and mixed populations (children and adults).
†Cross-over trial
§Flash glucose monitoring with FreeStyle Libre device which differs from traditional CGM (all other trials included in this report evaluate traditional CGM devices); see report background and results sections for details regarding the differences between these devices.

Below is a summary comparing key findings from the 2011 and 2017 updated report. The 2011 report included only people ≤18 years of age with diabetes requiring insulin. Analysis of adult or pregnant patients with diabetes is included in this updated report but was not part of the previous report. Key findings for all populations are presented below.

Results Summaries Comparing Key Findings between the 2011 Report and the 2017 Update

Key Results From 2011 HTA Report	Results From This 2017 Updated Report
Evidence of efficacy and effectiveness of CGM: Patients ≤18 years of age **Reducing microvascular complications**: No evidence. **Reducing macrovascular complications**: No evidence. **Fetal outcomes, cesarean rates**: No evidence **Achieving target A1C levels**: There was LOW evidence that CGM improved the proportion of patients achieving A1C targets compared to SMBG. Two RCTs reported the proportions of patients achieving A1C targets: one found participants in the CGM group were roughly twice as likely to achieve A1C targets and the other found no statistically significant difference. Changes in A1C levels: There was LOW evidence that CGM resulted in a greater change in mean A1C compared to SMBG. Two RCTs reported differences between groups: one found no statistically significant difference and the other found a small difference of questionable clinical significance. **Maintaining A1C levels**: No evidence. **Acute episodes of hypoglycemia**: There was LOW evidence that CGM reduces episodes of hypoglycemia compared to SMBG. Two RCTs reported differences in hypoglycemic episodes and neither found statistically significant differences. **Hyperglycemia**: There was LOW evidence that CGM reduces episodes of hyperglycemia compared to SMBG. One RCT reported rates of hyperglycemia and did not find a statistically significant difference. **Episodes of ketoacidosis**: No evidence.	Evidence of efficacy and effectiveness of CGM: Patients ≤18 years of age **Reducing microvascular complications**: No evidence. **Reducing macrovascular complications**: No evidence. **Fetal outcomes, cesarean rates**: No evidence **Achieving target A1C levels**: Achieving HbA1c % of <7% was more common in children with CGM versus SMBG in one trial at 3 months (SOE Low) but no clear difference was seen across two trials at 6 or 12 months. (SOE: Moderate) **Changes in A1C levels:** Across parallel RCTs, small reductions from baseline in mean HbA1c % favoring CGM over SMBG was seen at 3 and 6 months but pooled estimates failed to reach statistical significance. At 12 months there was no clear difference between CGM and SMBG; one trial reported a clinically and statistically significant difference favoring CGM, while another did not; the pooled estimate was not statistically significant. However, one cross over trial reported a significant reduction in mean HbA1C % favoring CGM across both 6 month treatment periods. (SOE: low for 3 months, moderate for 6 and 12 months) **Maintaining A1C levels**: No clear difference between CGM and SMBG was seen across trials reported results at 12 months. (SOE moderate). Specific comparative evaluation of maintenance of A1C levels was not reported. **Acute episodes of hypoglycemia**: There was no apparent difference between CGM and SMBG with regard to various measures or hypoglycemia. There were no differences between groups for proportion of children with ≥1 severe hypoglycemic events, the number of severe events, and number of severe

Key Results From 2011 HTA Report	Results From This 2017 Updated Report
Quality of life: There was LOW evidence that CGM improves quality of life. One RCT reported results of QOL measures and did not find any statistically significant differences. **Safety of CGM**: There was MODERATE evidence regarding the safety of CGM. No major adverse events were reported The most frequent problems included: redness/itching, dry skin, mild and moderate acute skin changes, and irritation. There were no deaths reported in any study. **Long term and short term cost-effectiveness:** No evidence	hypoglycemic events with seizure, coma or loss of consciousness or incidence of severe hypoglycemia at any time frame. Studies were likely underpowered to detect differences. (SOE Low) **Hyperglycemia:** Across two parallel design RCTs, results suggest that at 3and 6 months children may have spent fewer minutes per day in a hyperglycemic range of >180mg/dL, or in a severe hyperglycemic range (<250mg/dL) while using CGM, however, there is substantial variability in the estimates (wide confidence intervals) which suggests that estimates are not stable for this indirect outcome **Quality of Life**: Across three parallel design RCTs, there were no differences between CGM and SMBG in children's self-ratings and in parent's proxy rating across a number of generic and disease specific measures of quality of life, with the exception of Hypoglycemia Avoidant Behavior scores (HFS subscale) which improved more in parents of children using CGM in one trial. The one cross-over trial reported similar results. **Episodes of ketoacidosis**: No evidence. **Safety of CGM**: There were no trials that specifically evaluated safety in children. One trial did report that two children experienced a serious device-related complication (cellulitis related to sensor use/insertion). In general, discontinuation of CGM use was reported by six trials including both children and adults due to difficulty using the device and alarm frequency. Nonsevere device-related adverse events, primarily skin problems/irritation was a common occurrence across the trials. **Long term and short term cost-effectiveness**: None of the economic studies that met the inclusion criteria for the update report evaluated the cost-effectiveness of CGM in children specifically.

KQ1 Summary of Results:

General findings for each diabetes type for the primary outcomes are briefly summarized by age group below. The strength of evidence tables that follow provide information on effect sizes, general conclusions and additional information for the primary outcomes and list the trials that contributed to the conclusions. Detailed findings, including results for secondary outcomes, are found in the full report. None of the included studies reported on the primary clinical outcomes of interest. We report following primary intermediate outcomes and the overall strength of evidence here:

- HbA1c % (success measures and mean change)
- Hypoglycemia
- Fetal outcomes, caesarean section rate

For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. Half of the trials were moderately low risk of bias and half were moderately high risk of bias; assessment details are provided in the full report. The overall strength of evidence for most efficacy outcomes was considered low across interventions and comparators. The strength of evidence tables below and more detailed strength of evidence evaluation in Section 5 of the report provide additional information. References and related data for the studies in the bulleted Key Points are included in the Summary of Evidence tables.

Few trials using newer CGM devices were identified and were in adult populations. No trials in those <18 years old using newer devices were identified. The following trials employed newer CGM technology: Beck 2017a (T1DM) Beck 2017b (T2DM), Lind 2017, van Beers 2016, Bolinder 2016 and Haak 2016. Many of the trials incorporating older devices are considered pivotal trials and still provide a basis for guidelines and consensus statements. The full report and appendices provide detail on newer and older devices.

Children with T1DM

None of the trials in persons <18 years old employed newer CGM devices. Mean baseline HbA1c% in most trials was ~8%; one trial reported a value of 11.3%.

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:

HbA1C %

- Achieving HbA1c % of <7% was more common in children with CGM versus SMBG in one trial at 3 months (SOE Low) but no clear difference was seen across two trials at 6 or 12 months (SOE Moderate). Similarly, at 3 months more children using CGM had an absolute reduction in HbA1c% of ≥ 0.5% in one trial however at 6 months across two trials there was no clear difference. (SOE Low).
- CGM was not associated with clinically or statistically significant improvement in mean HbA1c across included trials. Across three parallel RCTs, a small reduction from baseline in mean HbA1c

% favoring CGM over SMBG was seen at 3 months. At 6 months pooled estimates failed to reach statistical significance. At 12 months there was no clear difference between CGM and SMBG; one trial reported a clinically and statistically significant difference favoring CGM, while another did not; the pooled estimate was not statistically significant. However, one cross over trial reported a significant reduction in mean HbA1C % favoring CGM across both 6 month treatment periods. (SOE Low for 3 months, Moderate for 6 and 12 months)

Hypoglycemia

- **Severe hypoglycemic events**: Studies were likely underpowered to detect differences between treatments for this rare event, contributing to the findings of no apparent difference between CGM and SMBG with regard to the proportion of children with ≥1 severe hypoglycemic events, the number of severe events, and number of severe hypoglycemic events with seizure, coma or loss of consciousness or incidence of severe hypoglycemia at any time frame. (SOE Low)
- **Hypoglycemia (<70 mg/dL):** There were no differences between CGM and SMBG with regard to the minutes per day spent in at this hypoglycemic range or area under the curve (AUC) across two trials. (SOE Low)
- **Hypoglycemia (<55 mg/dL):** There were no differences between CGM and SMBG with regard to the minutes per day spent in at this hypoglycemic range across two trials at 3 or 6 months. (SOE Low)

Other outcomes (strength of evidence not assessed, please see full report for additional detail)

- **Adherence:** Single arm (case series) extensions of included trials generally found that greater CGM adherence/use was associated with better HbA1c levels in children over 6 to 12 months of follow-up but no difference in time spent in hypoglycemic ranges based on adherence.
- **Quality of life and satisfaction** In general, there were no statistical differences between children who used CGM and those who performed SMBG only in self-ratings and in parent's proxy ratings across a number of generic and disease specific measures of quality of life. Hypoglycemia Avoidant Behavior scores (HFS subscale) improved more in parents of children using CGM compared with SMBG alone as well as greater satisfaction in both children and parents in the CGM versus SMBG group on Insulin Delivery System Rating Questionnaire measures in one trial. More frequent CGM use was associated with greater satisfaction among children and their parents in another trial.

Adults with T1DM

Results are for traditional CGM devices (those with automatic alarms) are reported unless otherwise noted. Results for flash CGM devices are reported separately. In most traditional CGM trials, baseline HbA1c % was >8%. The baseline HbA1c% was <7% in the single trial of flash CGM.

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:
HbA1C %

- Traditional CGM: Achieving HbA1c % of <7% was significantly more common in adults with TCGM use versus SMBG at 3, 6 across two trials and at 12 months in one trial (SOE Low at all times). Similarly, across two trials, more CGM recipients experienced an absolute HbA1c reduction of >0.5% versus SMBG (SOE Moderate) at 3 months and across two trials CGM was associated with a greater proportion of persons with a relative reduction of >10% in HbA1c than SMBG compared with baseline at 3 and 6 months (SOE Low). Across trials, the bulk of the evidence suggests clinically meaningful improvement in mean HbA1c % with CGM versus SMBG. (SOE Low) Findings from two trials of the three trials using newer devices were generally consistent (favoring CMG) to those from other trials for most HbA1c outcomes. One cross-over trial using newer devices found no difference between groups for mean A1c.
- Flash CGM: There were no differences in mean HbA1c between FCGM and SMBG at 3 or 6 months, however baseline values were <7% in both groups. (SOE Insufficient)

Hypoglycemia

- **Severe hypoglycemic events**: Studies were likely underpowered to detect differences between treatments for this rare event.
    - Traditional CGM**:** Across three parallel RCTs, there were no apparent differences between CGM and SMBG at across time points up to 12 months in the proportion of adults experiencing ≥ 1 severe hypoglycemic events or in the number of severe hypoglycemic events across 4 trials. Similarly, in one cross-over trial there was no difference in the proportion of adults experiencing ≥ 1 severe hypoglycemic event for CGM and SMBG phases after adjustment for study duration. Three of the four cross-over trials reported no difference between the phases in the numbers of events. Studies may have been underpowered to detect differences (SOE Low).
    - Flash CGM: There were no differences between FCGM and SMBG (SOE: Insufficient)
- **Hypoglycemia (<70 mg/dL):**
    - Traditional CGM: Across parallel and cross-over trials, CGM appears to be associated with decreased time spent in this range, however, the clinical significance of the effect sizes is unclear. (SOE Low) There is no clear difference between CMG and SMBG with regard to number of events standardized across days of monitoring with conflicting results between one parallel trial and one crossover trial. (SOE Low)
    - Flash CGM: FCGM was associated with decreased time spent in this hypoglycemic range and number of events compared with SMBG. (SOE: Insufficient)
- **Hypoglycemia (<55 mg/dL)**
    - Traditional CGM: As small decrease in the mean minutes per day spent in this range favoring CGM was seen at 3 months (SOE Low), but was no longer significant at 6 months (SOE Insufficient) where substantial heterogeneity was noted; results from the trial using newer devices failed to reach statistical significance.
    - Flash CGM: FCGM was associated with decreased time spent in this hypoglycemic range (SOE: Insufficient)

- **Nocturnal hypoglycemia:**
    - Traditional CGM: One parallel trial and one cross over trial suggest that the percent of time spent in hypoglycemic range of <70mg/dL at night was statistically less for CGM versus SMBG (SOE Low). Similarly in the parallel trial, the median percent of time spent in the severe hypoglycemic range (<50 mg/dL) was also less in the CGM group versus the SBMG group. (SOE Insufficient). The clinical importance of sone effect sizes is unclear.
    - Flash CGM: FCGM was associated with less time in the hypoglycemic ranges and fewer events. (SOE Insufficient).

Other outcomes (strength of evidence not assessed, see full report and appendices for details)

- Adherence: Single arm (case series) extensions of included trials generally found that greater CGM adherence/use was associated with better HbA1c levels
- Quality of life measure and satisfaction: Results varied across various quality of life measures as reported three parallel design RCTs and two cross over trials. In general, CGM use was associated with greater improvement on the Diabetes Treatment Satisfaction Questionnaire (DTSQ) versus SMBG across two cross-over trials, one of which used a newer device. More frequent CGM use was associated with greater satisfaction among children and their parents in an older trial. The one trial of flash CGM reported significantly improved satisfaction for FCGM versus SMBG.

Mixed populations (adults and children) with T1DM

Trials were approximately 50% children, 50% adults. None of the trials used newer devices. Baseline HbA1c% ranged from 6.4% to 9.6%.

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:

HbA1C %

- Achieving HbA1c % of <7% was significantly more common in adults with CGM use versus SMBG at 3months across 3 trials (SOE Low) but not at 6 months across 2 trials (SOE Low). Small reduction from baseline in mean HbA1c % favoring CGM was seen at 3 months (3 trials) and 6 months (4 trials), but may not be clinically important. One cross over trial also reported a reduction favoring CGM following 6 month CGM periods. (SOE Moderate at both times)

Hypoglycemia

- **Severe hypoglycemic events**: Studies were likely underpowered to detect differences. There were no differences at any time frame up to 6 months between CGM and SMBG with regard to the proportions for patients experiencing severe hypoglycemic events, the number or rates of events. Similarly, there was no difference between groups in the number of severe hypoglycemic events with seizure, coma or loss of consciousness or for events requiring intervention or assistance. (SOE Low for all outcomes)

- **Hypoglycemia (<70 mg/dL):** There were no differences in number of events, minutes/day or percent of time spent in this range between CGM and SMBG at 3 months. A 16 minute difference favoring CGM was seen across four trials at 6 months. The clinical significance of the effect size is not clear.
- **Hypoglycemia (<55 mg/dL):** There were no differences in minutes/day spent in this range between CGM and SMBG at 3 months or 6 months. (SOE Low)
- **Nocturnal hypoglycemia:** One parallel trial reported no difference between CGM and SMBG in the number of excursions below 55 mg/dL or 63 mg/dL. (SOE Insufficient)

Other outcomes (strength of evidence not assessed, please see full report for additional detail)

- **Adherence:** Among those using CGM, greater adherence to sensor use was associated with improved mean HbA1c at follow-up
- **Quality of life and satisfaction:** None of the included RCTs or observational studies reported quality of life in mixed populations of children and adults with T1DM.

Adults with T2DM

One of the four trials of traditional CGM in this population used newer CGM technology. One trial of flash CGM was included. Mean baseline HbA1c% values for all trials were ≥ 8.3%

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:

HbA1C %

- Traditional CGM: In one trial using newer devices, achieving HbA1c % of <7% was more common in adults with CGM use versus SMBG at 3 months but failed to reach statistical significance; no differences between groups was seen at 6 months. Significantly more CGM patients achieved ≥0.5% reduction in HbA1c at 3 and 6 months, however. (SOE Low for both outcomes and time points) More CGM patients achieved a clinically and statistically significant reduction from baseline in mean HbA1c % favoring CGM over SMBG at 3 months (3 trials, SOE Moderate). At 6 months the difference was statistically significant but may not be clinically significant. (3 trials, SOE Low); the difference was not statistically significant at 9.5 and 12 months in one small trial (SOE Insufficient at 9, 12 months). Effect estimates from the trial incorporating newer devices were somewhat smaller, but generally consistent with those using older technology.
- Flash CGM: There was no difference between FCGM and SMBG at 6 months. (SOE Insufficient)

Hypoglycemia

- **Severe hypoglycemic events:** Studies were likely underpowered to detect differences.
    - Traditional CGM**:** Severe hypoglycemic events were rare as reported by two trials. There was no difference between CGM and SMBG with regard to the proportion of patients experiencing an episode of severe hypoglycemia over 3 and 6 months follow-up in two trials; data were generally poorly reported for this outcome (SOE Low).

  - Flash CGM: Severe hypoglycemic events were rare and not different between groups. (SOE Insufficient)
- **Hypoglycemia (<55 mg/dL)**:
  - Traditional CGM: No between-group differences were reported for minutes per day, % of readings per day, or % of time spent in the <50 mg/dL range in two trials, one of which used newer technology or at 6 months in this later trial. (SOE Low).
  - Flash CGM: Significantly fewer minutes per day were spent in hypoglycemic range <55 mg/dl in the FCGM vs. SMBG group. (SOE Insufficient)

- **Hypoglycemia (<70 mg/dL)**
  - Traditional CGM: No between-group differences were reported for minutes per day, % of readings per day, or % of time spent in the <70 mg/dL range in two trials, one of which used newer technology at 3 months or at 6 months in this later trial. (SOE Low).
  - Flash CGM: Significantly fewer minutes per day were spent in hypoglycemic range <70 mg/dl in the FCGM vs. SMBG group. (SOE Insufficient)

- **Nocturnal hypoglycemia**
  - Traditional CGM: No between-group differences were reported for minutes per day, % of readings per day, or % of time spent in the <70 mg/dL range in two trials, one of which used newer technology at 3 months or at 6 months in this later trial. (SOE Low).
  - Flash CGM: Significantly fewer minutes per night were spent in hypoglycemic ranges <55 and <70 mg/dl in the CGM vs. SMBG group.

Other outcomes (strength of evidence not assessed, see full report for details)

- **Adherence:** Greater sensor usage was associated with greater reduction in HBA1c% up to 12 months in one trial.
- **Quality of life and satisfaction:** No differences were found between traditional CGM and SMBG in any of the quality of life measures assessed in the one trial which employed newer devices, in another trial of older devices or for most measures used in the trial of flash CGM. CGM usage was associated with improved satisfaction in trials of traditional CGM and flash CGM.

Women with diabetes during pregnancy

Pre-existing T1DM in pregnancy

Primary clinical and intermediate outcomes

- Statistically significant and clinically important differences in frequencies of caesarean section (2 trials, SOE Moderate) and newborn admission to neonatal intensive care units (1 trial, SOE Low) were found.
- No statistically significant differences were seen for the following outcomes. In some instances studies may have lacked sufficient statistical power

- Moderated evidence (2 RCTs): Gestational age; Birthweight; Miscarriage; Preterm Delivery; Preeclampsia
- Low SOE (1 or 2 RCTs depending on outcome): Large for gestational age; Episodes of severe neonatal and severe maternal hypoglycemia; Hypoglycemia (neonatal, maternal); Still birth; Birth trauma; and HbA1c% measures (success, ≤6.5%; mean change from baseline)
- Insufficient evidence (1 or 2 RCTs depending on outcome): (1 or 2 RCTs depending on outcome): Major congenital anomalies; Time spent in hypoglycemia (≤70 or <63 mg/dl range)

Other outcomes (strength of evidence not assessed)

- Quality of life measures: There were no statistical differences between pregnant women with pre-existing T1DM who used CGM versus those who performed SMBG only on any of the patient-reported measures assessed in one trial: Blood Glucose Monitoring System Rating Questionnaire (BGMSRQ), Problem Areas in Diabetes (PAID), ShortForm-12 questionnaire, and Hypoglycaemia Fear Survey (HFS II).
- Satisfaction: Mean satisfaction scores on the CGM Satisfaction Scale (CGM-SAT) indicated overall favorable ratings with CGM use in one trial.

Pre-existing T2DM in pregnancy

Primary clinical and intermediate outcomes

- There is insufficient evidence from one very small trial to draw firm conclusions for any outcome. Small sample size likely contributed to finding no differences between CGM and SMBG for any outcome (SOE Insufficient).

Gestational diabetes

Primary clinical and intermediate outcomes

- There is insufficient evidence from one very small trial to draw firm conclusions for any outcome. Small sample size likely contributed to finding no differences between CGM and SMBG for any outcome (SOE Insufficient).

KQ2: Summary of adverse events and safety

Data across all patient populations were considered together. Events are only reported for CGM.

Inconsistent definitions, classifications and poor reporting of adverse events make it difficult to draw meaningful conclusions. There are limited data on newer devices. Most adverse events reported are sensor-related or senor-related skin problems. Events are detailed in the full report and appendices. For traditional CGM devices, SOE is low for all outcomes. Definitions and reporting of adverse events and symptoms were poor in trials of flash CGM and evidence was considered insufficient.

- **Serious device related adverse events:** Relatively rare across nine trials of traditional CGM (0% to 7%) and included insertion site infections resulting in cellulitis and skin abscess, serious skin reactions, hospitalization for ketoacidosis (including one case caused by pump failure). Two trials with newer devices report 0%-1% of patients experiencing such events. (SOE Low) Trials for flash CGM report 1%to 3% of participants experienced serious AEs related to sensor site and skin-related problems but provide no information on severity of these. (SOE Insufficient) Sample sizes were likely too small to detect rare outcomes.
- **Adverse events leading to discontinuation:** Discontinuation due to device-related adverse events was not uncommon across 6 RCT (2% to 24%). Most patients stopped CGM use due to difficulty operating the device, frequency of alarms (bothersome), or discomfort/inconvenience. Observational studies reported discontinuation of 44%-61% for similar reasons. Two trials of newer devices report discontinuation for allergic reaction (1%) and difficulty in uploading data (4%).(SOE Low) Trials of flash CGM report frequency of discontinuation in 2% to 5% of patients related to site allergic reaction, necrosis, infection, rash, pain, erythema and itching (SOE Insufficient).
- **Non-serious device-related adverse events:** Non-serious device related adverse events are common with CGM use and are primarily comprised of skin-related problems at the sensor or insulin infusion site (e.g., erythema, inflammation, rash/allergic reaction, itchiness, mild infection). Reported frequencies in non-pregnant populations ranged from 0 to 24% across RCTs and were reported at 36% in one cohort study. (SOE Low) Trials of flash CGM report "expected sensor-insertion site symptoms" (not considered AEs by the authors) in up to 40% of subjects but do not provide information regarding the distinction between events (reported as 4% to 8%) and symptoms.
- **Technical or mechanical issues:** Technical or mechanical issues reported by three RCTS included technical problems with sensor leading to loss of all glucose readings, unspecified mechanical problems, and "device issue"(in one trial of newer technology)(SOE Low)

KQ 3. Summary Differential Efficacy and Harms:

- In one trial of adults with T1DM, none of the baseline factors analyzed (baseline HbA1c, age, percent of CGM time <70 mg/dl, SMBG frequency, education, hypoglycemia unawareness and fear, diabetes numeracy score, and clinical site) modified the effects of CGM for the outcome of change in HbA1c from baseline in one moderately low risk of bias trial. Sample sizes in this trial were likely inadequate to effectively test for modification. (SOE Insufficient)
- In one trial of adults with T2DM by the same authors suggests that hypoglycemic awareness or uncertainty may modify the effect of CGM on change in baseline HbA1c%. None of the other exposures appeared to modify the association with change in HbA1c%. Sample sizes in this trial were likely inadequate to effectively test for modification. (SOE Insufficient)

KQ 4. Summary of Economic Studies

- Five cost-utility analyses (CUA) in adults evaluated the cost effectiveness of CGM versus SMBG, four of which were in adults with type 1 DM and one in adults with type 2 DM. Four studies were funded by industry. Only one included data based on newer devices. Assumptions regarding baseline HbA1c% and changes resulting from CGM use differed across studies. Quality of studies overall was moderately good to good (QHES scores 75 to 92). No full economic studies related to use of CGM in persons <18 years old or in pregnancy were identified.
- Adults with type 1 DM: 2 Two CUA were conducted in the U.S, one in Canada and one in Sweden. All claimed a societal perspective; however one did not provide information on indirect cost. In general, all concluded that CGM may be cost-effective.
    - Base case ICERs across studies of adults with type 1DM ranged from $43,926/ QALY to $98,679/QALY. Ranges from sensitivity analyses ranged from $42,552/QALY to over $700,000/QALY. Across studies, authors concluded that CGM may be cost-effective at a willingness to pay of $50,000 to $100,000.
    - Limitations:
        - Models assumed a long-term horizon (>30 years). RCT data for CGM use in included trials is reported for up to 12 months for older devices, 6 months for newer devices.
        - Results from modeling long term outcomes using hypothetical cohorts, as three of the studies relied solely on, are largely dependent on the assumptions used in selecting the parameters, only some of which were addressed or reported in sensitivity analysis.
        - Sensitivity analysis related to model assumptions for long-term micro and macrovascular disease is poorly presented across studies and the impact on cost-effectiveness is unclear across studies; Two studies that evaluated such complications more extensively reported greater variability in estimated cost-effectiveness. Modeling of CGM adherence and other “real-life” factors are not presented in sensitivity analyses.
- Adults with type 2 DM not taking prandial insulin: One CUA conducted in the U.S. using UK trial data from a payer perspective reported ICER of $8,898 /QALY.
    - Probabilistic cost-effectiveness analysis suggests that the likelihood of the intervention being cost-effective is 70% at the willingness-to-pay threshold of $100 000 per QALY over a lifetime time horizon based modeling of a hypothetical cohort.

Study limitations included every limited sensitivity analyses, modeling of life-time use (limited long-term data in adults with type 2 diabetes, use of older CGM devices. It is unclear if the data in models for complications from older diabetes treatment and the Framingham study reflect current care.

Strength of Evidence Summaries

The following summaries of evidence for primary outcomes have been based on the highest quality of studies available. ***Detailed SoE tables, including reasons for downgrading are found in section 5 of the report***. Additional information on lower quality studies and secondary outcomes is available in the report. Summaries for each key question are provided in the tables below and are sorted by type of diabetes and age. Details of other outcomes are available in the report.

Key Question 1: Strength of Evidence Summary: Efficacy Results

CGM versus SMBG efficacy results in children with type 1 diabetes

Outcome	Follow-up	RCTs	Reasons for Downgrading	Conclusion	Quality
Success (Achieving HbA1C% <7.0%)	3 mos	1 (N=113) JDRF 2008	Inconsistency (unknown) Imprecision (-1)	GCM 25%, SMBG 6.9% RD -19%, 95% CI -32% to -5% Conclusion: Substantially more children in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW
	6 mos	2 (N = 251) JDRF 2008, Mauras 2012	Imprecision (-1)	GCM 20.8%, SMBG 13.5% Pooled RD 7%, 95% CI -21% to 6%, I^2 = 50% Conclusion: No clear differences between CGM and SMBG.	⊕⊕⊕◯ MODERATE
	12 mos	2 (N = 309) Bergenstal 2010 Kordonuri 2010	Imprecision (-1)	GCM 26.0%, SMBG 19.4% Pooled RD 7%, 95% CI -15% to 0%, I^2 =0% Conclusion: No clear differences between CGM and SMBG.	⊕⊕⊕◯ MODERATE
HbA1c%: Absolute reduction of ≥0.5%	3 mos. 6 mos	1 (N=113) JDRF 2008 2 (N = 141) JDRF 2008 Mauras 2012	Inconsistency (3 mos. unknown; 6 mos., -1) Imprecision (-1)	3 months (1 trial) GCM 47%, SMBG 28% RD -20%, 95% CI -37% to -2%) 6 months (2 trials) GCM 35%, SMBG 31% Pooled RD -6%, 95% CI-37% to 25%, I^2 = 87% Conclusion: At 3 months, more children with CGM had an absolute reduction in HbA1c% of ≥ 0.5%, however at 6 months across two trials there was no difference in the pooled	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reasons for Downgrading	Conclusion	Quality
				estimate and heterogeneity was substantial.	
HbA1c %: relative reduction of ≥10% from baseline	3, 6 months	1 (N=113) JDRF 2008	Inconsistency (unknown) Imprecision (-1)	3 months: RD -19%, 95% CI -34% to -4% 6 months: RD -17%, 95% CI -31% to -2% Conclusion: More children in the CGM group experienced ≥10% reduction at 3 and 6 months	⊕⊕◯◯ LOW
HbA1c % Mean between group difference in change from baseline	3mos	3 (N= 307) Kordonouri, Hirsch 2008, JDRF 2008	Inconsistency (-1) Imprecision (-1)	Pooled MD in change scores -0.22%, 95% CI -0.44% to 0.0%, I^2 = 3% Conclusion: Small reduction from baseline in mean HbA1c% favoring CGM was not statistically significant	⊕⊕◯◯ LOW
	6 mos	4 parallel RCTs (N = 445) Hirsch 2008, JDRF 2008 Kordonouri 2010 Mauras 2012 1 Crossover RCT (N=72) Battelino 2012	Inconsistency (-1)	Pooled MD in change scores: (4 parallel trials): -0.90, 95% CI -0.26 to 0.08; Cross-over trial: MD -0.46, 95% CI -0.26 to -0.66 Conclusion: There is no clear difference between CMG and SMBG across the parallel RCTs which provide the bulk of the evidence. One cross-over trial reported a significant difference during CMG periods: MD -0.46, 95% CI -0.26 to -0.66	⊕⊕⊕◯ MODERATE
	12 mos	2 (N=310) Bergenstal 2010, Kordonouri 2010	Imprecision (-1)	Pooled MD in change scores: -0.31, 95% CI -0.99 to 0.36, I^2 = 73% Conclusion: There is no difference between CGM and SMBG based on pooled estimates; substantial heterogeneity is noted.	⊕⊕⊕◯ MODERATE
Hypoglycemia (≤70 mg/dL) Minute/day in range	3 mos, 6 mos	2 (N =239) JDRF 2008 Mauras 2012,	Indirectness (-1) Imprecision (-1)	**3 months:** Pooled WMD: -5.22, 95% CI -32.78 to 22.35 **6 months:** Pooled WMD: -11.09, 95% CI -30.16 to 7.99 Conclusion: There is no clear difference between CGM and SMBG at any time up to 6 months	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reasons for Downgrading	Conclusion	Quality
Hypoglycemia (<55 mg/dL) Minute/day in range	3 mos, 6 mos	2 (N =239) JDRF 2008 Mauras 2012,	Indirectness (-1) Imprecision (-1)	**3 months:** Pooled WMD: -3.04, 95% CI-10.93 to 4.48 **6 months:** Pooled WMD: -2.48 95% CI -10.49 to 5.53 <u>Conclusion:</u> There is no difference between CMG and SMBG at either time.	⊕⊕◯◯ LOW
Hypoglycemia (≤70 mg/dL) AUC	3, 6, 12 mos	3, 6 months 1 (N= 128) Mauras 2012) 12 mos 1(N=159) Bergenstal 2010	Indirectness (-1) Imprecision (-1)	CGM vs. SMBG **3 months:** 0.1 vs. 0.2 **6 months:** 0.1 vs. 0.2 **12 months:** 0.23 vs. 0.25, p = 0.790 <u>Conclusion:</u> There is no difference between CGM and SMBG at any time up to 12months	⊕⊕◯◯ LOW
<u>Severe Hypoglycemic events</u> (Events requiring assistance, resuscitative action, those resulting in loss of consciousness, seizure, or coma)	To 12 mos	4 trials (N = 517) JDRF 2008, Mauras 2012, Bergenstal 2010 Kondnouri 2010	Imprecision (-2)	CGM vs. SMBG Number of events: 4.6% vs. 6.5%; pooled RD -1.2%, 95% CI -6% to 2.0%, I^2 = 22% <u>Conclusion across measures</u>: Severe hypoglycemia is a rare event and studies were likely underpowered to detect differences between treatments No apparent difference between CGM and SMBG with regard to the number of severe events; Similarly no difference between groups in the following measures: the proportion of children with ≥1 severe hypoglycemic events, number of severe hypoglycemic events with seizure, coma or loss of consciousness or incidence of severe hypoglycemia at any time frame..	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

CGM versus SMBG efficacy results in adults with type 1 diabetes

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
Success (Achieving HbA1C% <7.0%	3 months	2 (N=253) Beck 2017, JDRF 2008	Inconsistency (-1) Imprecision (-1)	CGM 23%, SMBG 8.2% Pooled RD -18%, 95% CI -40% to 3.0%, I^2 = 81% Conclusion: More adults in the CGM group achieved success vs. SMBG; while pooled results did not reach statistical significance, results from individual trials did. Substantial heterogeneity is noted.	⊕⊕◯◯ LOW
	6 months	3 (N=328) Beck 2017, JDRF 2008, Hermanides 2011	Inconsistency (-1) Imprecision (-1)	CGM 25.4%, SMBG 4.4% Pooled RD -23%, 95% CI -36% to -10%, I^2 = 67% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW
	12 months	1 (N=329) Bergenstal 2010	Inconsistency (unknown) Imprecision (-1)	CGM 34% , SMBG 11.7% RD -23%, 95% CI -31% to -14% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW
HbA1c %: Absolute reduction of ≥0.5	3 months	2 (N=243) JDRF 2008, New 2015	Imprecision (-1)	CGM 32.9%, SMBG 14.9% Pooled RD -18%, 95% CI -28% to -8%, I^2 = 0% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕⊕◯ MODERATE
	6 months	1 (N=114) JDRF 2008	Inconsistency (unknown) Imprecision (-1)	CGM 48%, SMBG 11% RD -37%, 95% CI -54% to -21% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW
HbA1c %: relative reduction of ≥10% from baseline	3, 6 months	2 (N=353) Beck 2017, JDRF 2008	Inconsistency (3 mos., -1) Imprecision (-1)	**3 months:** CGM 48.4%, SMBG 18.4% Pooled RD -25%, 95 CI% -50% to 0%, I^2 = 82% **6 months:** CGM 46.7%, SMBG 12.1% Pooled RD -30%, 95% CI -46% to -13%, I^2 =64%	3 months ⊕⊕◯◯ LOW 6 months ⊕⊕⊕◯ MODERATE

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
				Conclusion: More adults in the CGM group achieved success vs. SMBG at both timepoints; however, the results at 3 months are marginally significant	
HbA1c % Mean between group difference in change from baseline	3-4 months	6 (N=599) Beck 2017, Hermanides 2011, Hirsch 2008, JDRF 2008, New 2015, Peyrot 2009	Inconsistency (-1) Imprecision (-1)	Pooled MD in change scores: : -0.43%, 95%CI -69% to -19%, I^2=76% Conclusion: CGM use was associated with clinically and statistically significant improvement in mean HbA1c % compared with SMBG	⊕⊕◯◯ LOW
	3 months	Flash CGM 1 (N=239) Bolinder	RoB (-1) Inconsistency (unknown) Imprecision (-1)	FCGM 0.1% (SD 0.6), SMBG 0.1% (SD0.7%) MD 0%, 95% CI -0.17% to 17% Conclusion: No differences between FCGM and SMBG	⊕◯◯◯ INSUFFICIENT
	6 months	4 (N = 429) Beck 2017, Hermanides 2011, Hirsch 2008, JDRF 2008,	Inconsistency (-1) Imprecision (-1)	Pooled MD in change scores -0.52%, 95% CI -0.84% to -0.19%, I^2 = 84% Conclusion: CGM use was associated with clinically and statistically significant improvement in HbA1c % compared with SMBG	⊕⊕◯◯ LOW
		Flash CGM 1 (N = 239) Bolinder	RoB (-1) Inconsistency (unknown) Imprecision (-1)	FCGM 0.2% (SD0.6) SMBG 0.2% (SD 0.7) MD 0%, 95% CI -0.17% to 17% Conclusion: No differences between FCGM and SMBG	⊕◯◯◯ INSUFFICIENT
	12 months	1 (N=329) Bergenstal 2010	Inconsistency (unknown) Imprecision (-1)	Pooled MD in change scores: 0.6%, 95% CI -0.76% to -0.44% Conclusion: CGM use was associated with clinically and statistically significant improvement in HbA1c % compared with SMBG	⊕⊕◯◯ LOW
HbA1c % Mean difference at follow-up	Longest follow-up†	Parallel RCTs 6 (n= 785) JDRF 2008, Bergenstal 2010, Hirsch	Inconsistency (-1) Imprecision (-1)	Parallel trials (6 trials, N=785) Pooled MD -0.48, 95% CI -0.7 to -0.28, I^2 = 79%	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
		2008, Hermanides 2011, Peyrot 2009 Beck 2017, New 2015 Cross-over trials 4 (N = 305) Battelino 2012, Lind 2017 vanBeers 2016, Langeland 2012		Cross-over trials (26 week treatment period, 2 trials, N=223) Pooled MD -0.42, 95% CI -0.51 to -0.33, I^2 = 0% Cross-over trials (4-16 week treatment, 2 trials (N=82) Pooled MD 0.06, 95% CI -0.05 to 0.16, I^2 = 0% Conclusion: Across trials, the bulk of the evidence suggests clinically meaningful improvement in mean HbA1c % with CGM versus SMBG.	
# of hypoglycemic events (standardized per day in parallel trial, events/week in cross-over trial)	Parallel trial 6 mos Cross-over trial 4 month treatment periods	Parallel 1 RCT (N = 71) Hermanides Crossover 1 (n=52) vanBeers	Inconsistency (-1) Indirectness (-1) Imprecision (-1)	Parallel trial CMG 0.7 ± 0.7 SMBG 0.6 ± 0.7 MD 0.1, 95% CI -0.2 to 0.5 Crossover trial Events/week(CGM-derived data): 10.1 (8.7 to 11.4) vs. 11.1 (9.8 to 12.5), MD -1.1, 95% CI -1.4 to -0.8 Conclusion: There is no clear difference between CGM and SMBG in one parallel trial; one cross-over trial reported fewer events per week during CGM phases; the clinical significance of these findings is unclear.	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (<70 mg/dL) Minute/day in range, hours/day or % of time spent in range, # of events	Parallel 3, 6 mos Cross-over, 4, 6 mos treatment periods	Parallel, 4 RCTs (N=448) JDRF 2008, Beck 2017, New 2015 Hemanides 2011 Cross-over RCTs 2 (N=213) Lind 2017, vanBeers 2016	Indirectness (-1) Imprecision (-1)	Parallel trials: Minutes per day **3 months** (2 trials, N=377): pooled MD -21.45 minutes, 95% CI -36.31 to -6.59, I^2 = 0%; **6 months** (2 trials, N=248): pooled MD -19.66 minutes, 95% CI -37.85 to -1.47, I^2 = 20% 1 Parallel trial (N = 71, <72mg/dL), 6 months: % time during monitoring: MD 0.2, 95% CI -1.4 to 1.9, p= 0.79; standardized number of events/day: MD 0.1 (-0.2 to 0.5, p = 0.40) 1 Cross-over trial (N=52):	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
				Hours per day across 16 week treatment periods: CGM 1.6 vs. SMBG 2.7 MD -1.1, 95% CI -1.4 to -0.8, p<0.0001; CGM-derived events/week: MD -1.1, 95% CI -0.14 to -0.8 1 Cross-over trial (N=142): % of time across 26 week treatment periods: CGM 2.79% ± 2.97% vs. 4.79% ± 4.03%, p <0.0001; MD -2.0, 95% CI -2.83 to -1.17 <u>Conclusion:</u> Across most parallel and cross-over trials, CGM appears to be associated with decreased time spent in the hypoglycemic range ≤70 mg/dL compared with SMBG.	
Hypoglycemia (≤70 mg/dL) Hours/day Number of events	3, 6 months	Flash CGM 1(N = 239) Bolinder 2016	RoB (-1) Inconsistency (unknown) Indirectness (-1)	<u>Hours/day, adjusted MD (SE)</u> 3 months: MD -1.09 (0.18) 6 months: MD -1.24 (0.24) <u># of events, adjusted MD (SE)</u> 3 months: MD -0.35 (0.09) 6 months: MD -0.45 (0.09) <u>Conclusion:</u> In 1 trial, FCGM appears to be associated with decreased time spent in the hypoglycemic range ≤70 mg/dL and number of events compared with SMBG	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (≤55 mg/dL) Minutes per day	3, 6 months	2 (N = 249) JDRF 2008, Beck 2017	Inconsistency (6 mos., -1) Indirectness (-1) Imprecision (-1)	**3 months:** Pooled MD -14.2 minutes, 95% CI -23 to -5.4 I^2=38% **6 months:** Pooled MD-13.1 minutes, 95% CI-30.4 to 4.25, I^2= 90% <u>Conclusion:</u> As small decrease in the mean minutes per day spent in this range favoring CGM was seen at 3 months, but was no longer significant at 6 months where substantial heterogeneity was noted; results from the newest	3 months ⊕⊕◯◯ LOW 6 months ⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
				trial failed to reach statistical significance.	
Hypoglycemia (≤55 mg/dL) Hours per day, number of events	3, 6 months	FCGM 1 RCT (N = 239) Bolinder	RoB (-1) Inconsistency (unknown) Indirectness (-1) Imprecision (-1)	Hours per day: **3 months:** adjusted MD -0.68, SE 0.13 **6 months:** adjusted MD -0.82, SE 0.74 Events **3 month:** adjusted MD -0.33, SE 0.06, **6 month:** adjusted MD -0.38, SE 0.74 Conclusion: In 1 trial FCGM appears to be associated with decreased time spent in the hypoglycemic range ≤55 mg/dL fewer events compared with SMBG	⊕◯◯◯ INSUFFICIENT
Severe hypoglycemia proportion of adults with ≥1 severe hypoglycemic event; number of events (Most trials defined as events requiring assistance or loss of consciousness)	Parallel 3-12 mos Crossover treatment periods of 4-26 weeks	Parallel 1 (N = 152) Beck 2017 3 Cross-over vanBeers 2016 (N= 52) Lind (N =161) Langeland (N=30)	Imprecision (-2)	Parallel Trials: Proportion of adults with ≥1 severe hypoglycemic events: 3 trials, pooled RD 0%, 95% CI -4% to 4%, I^2=0% Number of severe hypoglycemic events: 4 trials, pooled RD 0%, 95% CI-6% to 7%, I^2=46% Crossover trials: Proportion with ≥1 severe hypoglycemic event (1 trial, N = 52), adjusted OR 0.48, 95% CI 0.2 to 1.0, p=0.062; Number of events: Largest trial (n=161) CGM vs. SMBG phases, 1 event (0.04 per 1000 patient-years) vs. 5 events (0.19 per 1000 patient-years), p =0.7545; one small trial (N = 52) reported, fewer total events during CGM phases (14 vs. 34 events, p = 0.033); Mean number of episodes per 4 week treatment period (1 trial N=30) MD 0.9, 95% I -0.18 to 1.98, p=0.6 Conclusion: Studies were likely underpowered to detect	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
				differences between groups. Across parallel and cross-over trials there is no statistical difference between CGM and SMBG with regard to the proportion of adults with ≥1 severe hypoglycemic events. With regard to the number of events the bulk of evidence (4 parallel trials, 3 crossover trials) no statistical difference between groups for the number of severe hypoglycemic events was seen.	
Hypoglycemic severe adverse events; proportion of patients and number of events (appears to be defined as those requiring 3rd party assistance)	6 months	FCGM 1 RCT (N = 239)	RoB (-1) Inconsistency (unknown) Imprecision (-1)	FCGM 2% (n =2), SMBG 2% (n=3) of patients Number of events FCMG, 2, SMBG 4 Conclusion: There is insufficient evidence to draw conclusions; study was likely underpowered to detect rare events.	⊕◯◯◯ INSUFFICIENT
Nocturnal hypoglycemia; median percent of time spent at night in range, CGM-derived events	Parallel trial:6 mos, Crossover across both 16 week periods	Parallel 1 (N = 152) Beck 2017 Cross-over 1 (N= 52) vanBeers 2016	Inconsistency (<50 mg/dl, unknown) Indirectness (-1) Imprecision (<70mg/dL, -1 <50 mg/dL, -2)	CGM vs. SMBG <u>Parallel trial 6 months median % (IQR), effect estimates NR</u>: <70mg/dL median % (IQR): 1.8% (0.1% to 5.8%) vs. 5.2% (0.9% to 9.4%), p=0.003 <50 mg/dL: 0% (0% to 0.9%) vs. 0.3% (0% to 2.4%), p=0.001 <u>Cross-over trial, across both 16 week treatment periods, <70mg/dL:</u> % of time: 7.6% (95% CI 5.3% to 9.8%) vs. 13.3% (95% CI 11.0% to 15.5%); MD -5.7% 95% CI -8.2% to -3.2% CGM derived events/night: 0.26 (0.21 to 0.31) vs. 0.33 (0.28 to 0.38); MD -0.07, 95% CI -0.11 to -0.02	<70mg/dL ⊕⊕◯◯ LOW <50mg/dL ⊕⊕⊕◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
				Conclusion: Across parallel and cross-over trials, CGM appears to be associated with decreased time spent in the hypoglycemic ranges at night compared with SMBG, however, the clinical significance of the effect size is unclear.	
Nocturnal hypoglycemia; Mean Time in range Mean # of events	6 months	FCGM 1 RCT (N = 239)	RoB (-1) Inconsistency (unknown) Indirectness (-1) Imprecision (-1)	<70mg/dL, hrs/day adjusted MD (SE) **3 months**: -0.48 (0.10) **6 months:** -0.47 (0.12) Events: adjusted MD (SE) **3 months:** -0.11 (0.03) **6 months:** -0.14 (0.03) <55 mg/dL, hrs/day adjusted MD (SE) **3 months:** -0.68 (0.13) **6 months:** -0.82 (0.175) Events: adjusted MD (SE) **3 months:** -0.33 (0.06) **6 months: -**0.38 (0.074) Conclusion: FCGM was associated with less time in the hypoglycemic ranges and fewer events.	⊕⊕⊕◯ INSUFFICIENT

* Effect size are in the same direction

†Results based on longest reported follow-up for parallel trials (range 3-12 months); for cross-over trials, time is length of treatment periods (e.g. CGM phase, SMBG phase)

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

CGM versus SMBG efficacy results in mixed populations of adults and children with type 1 diabetes

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
Success (Achieving HbA1C <7.0%)	3 mos	3 (N=296) JDRF 2008 O'Connell 2009 Hirsch 2008	Inconsistency (-1) Imprecision (-1)	CGM 30 %, SMBG 11.3% Pooled RD -19%, 95% CI -32% to -7%, I^2=49% Conclusion: significantly more patients in the CGM group achieved success compared with SMBG	⊕⊕◯◯ LOW
	6 mos	2 (N = 251) JDRF 2008 Hirsch 2008	RoB (-1) Imprecision (-1)	CGM 16.9%, SMBG 21.4% Pooled RD 4%, 95% CI -6% to 14%, I^2= 0% Conclusion: No difference between groups.	⊕⊕◯◯ LOW
HbA1c %: Absolute reduction of ≥0.5% OR relative reduction of ≥10% from baseline	3, 6 months	1 (N=107) JDRF 2008	Inconsistency (unknown) Imprecision (-1)	Absolute reduction ≥0.5%: CGM 35.7% , SMBG 37.3 % RD 14%, 95% CI-33% to 4% Relative reduction, ≥10%: CGM 14% , SMBG 9.8% RD 4%, 95% CI-17% to 8% Conclusion: No difference between groups.	⊕⊕◯◯ LOW
HbA1c % Mean between group differences in A1c change from baseline	3 mos	Parallel trials 3 (N=269) JDRF 2008, Deiss 2006, O'Connell 2009	Imprecision (-1)	Pooled MD in change scores -0.25%, 95% CI -0.48% to -0.02%%, I^2 = 28% Conclusion: Small reduction from baseline in mean HbA1c % favoring CGM, but may not be clinically important	⊕⊕⊕◯ MODERATE
	6 mos	Parallel 4 (N=495) JDRF 2008, JDRF 2009, Battelino 2011, Raccah 2009 Crossover trial across 6 month treatment periods, 1 (n = 153)	Imprecision (-1)	Parallel trials: Pooled MD in change scores: -0.19%, 95% CI -0.34% to -0.04% 1 Crossover trial: MD across periods: -0.43, 95% CI -0.32 to -0.55 Conclusion: Small reduction from baseline in mean HbA1c % favoring CGM, but may not be clinically important	⊕⊕⊕◯ MODERATE
Severe Hypoglycemic	Up to 6 months	6 (N=656)	Imprecision (-2)	Patients with ≥ 1 event CGM 5.7% , SMBG 4.6%	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
events proportion of patients with ≥ 1 severe hypoglycemic events at any time frame; Number of severe events		Diess 2006, O'Connell 2009, JDRF 2008, JDRF 2009, Battelino 2011, Hirsch 2008		Pooled RD 1%, 95% CI -2% to 3%, I^2= 0% Number of events CGM 7.9%, SMBG 5.8% Pooled RD 1%, 95% CI- 2% to 3%, I^2= 29% Conclusion: Studies were likely underpowered to detect a difference between groups. No difference between groups for either outcome.	
Severe Hypoglycemia events requiring assistance or intervention	Parallel trials -3 months Cross-over 6 months	Parallel 3 (N =351) JDRF 2008, JDRF 2009, Raccah Crossover 1(N=153) Battelino 2012	Imprecision (-2)	Parallel Trials: CGM 3.4%, SMBG 2.9% Pooled RD 1%, 95% CI -3% to 3%, I^2=9% Crossover trial: events (rate) CGM 4 (5.7 per 100 patient-years) SMBG 2 (2.83 per 100-patient-years) P=0.40 Conclusion: Studies were likely underpowered to detect a difference between groups .No difference between groups	⊕⊕◯◯ LOW
Nocturnal Hypoglycemia	6 months	1 (N =116) Battelino 2011	Inconsistency (unknown) Indirectness (-1) Imprecision (-1)	CGM vs. SMBG (mean, SD) <55 mg/dL: 0.13 (0.30) vs. 0.19 (0.19), p=0.01 <63 mg/dL: 0.21 (0.32) vs. 0.30 (0.31), p=0.009 Conclusion: CGM was associated with fewer mean number of excursions vs. SMBG, <55 mg/dL and < 63 mg/dL; large standard deviations (substantial variability) are noted calling estimate stability into question. The clinical importance of these findings is unclear	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (<70 mg/dL)	3, 6 months	6 (N=645) JDRF 2008, JDRF2009, Battelino 2011, O'Connell 2009, Raccah 2009, Hirsch 2008	RoB (-1) Indirectness (-1) Imprecision (-1)	Minutes per day **3 months:** Pooled MD (2 trials, N= 226): -12.2, 95% CI-40.59 to 16.23, I^2=0% **6 months:** Pooled MD (4 trials N = 445)**:** -16.26, 95% CI-32.16 to -0.37, I^2=21% % of time spent in range, 1 RCT (N= 55), 3 months MD 0.54, 95% CI -3.5 to 4.6 Mean number of events, 2 RCTs (N= 254), 6 months:	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
				CGM 0.83 ± 0.73 vs. SMBG 0.84 ± 0.73 (1 trial) Ratio of means (1 trial): 0.70 (0.43 to 1.03) <u>Change in baseline # events per day, 1 RCT (N=100), 6 months</u> MD 0.0, 95% CI -0.3% to 0.3% <u>Conclusion:</u> There were no differences in number of events, minutes/day or percent of time spent in this range between CGM and SMBG at 3 months. A 16 minute difference favoring CGM was seen across four trials at 6 months. The clinical significance of the effect size is not clear.	
Time spent in hypoglycemic range < 55 mg/dL (min/day)	3, 6 months	3 months 2 (n=226) JDRF 2008, JDRF 2009 6 months 3 (N=345) JDRF 2008, JDRF 2009, Battelino 2011	Indirectness (-1) Imprecision (-1)	**3 months:** (2 trials) MD -7.83, 95% CI -15.92 to 0.26, I^2 = 0% **6 months:** (3 trials): MD -7.26, 95% CI-16.14 to 1.62, I^2 = 51% <u>Conclusion:</u> There were no differences minutes/day between CGM and SMBG at 3 or 6 months.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

CGM versus SMBG efficacy results in adults with type 2 diabetes

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
Success (Achieving HbA1c% <7.0%)	3 and 6 months	1 (N=152 at 3 months; N= 158 at 6 months) Beck 2017[b]	Inconsistency (unknown) Imprecision (-1)	**3 months:** CGM 22%, SMBG 12% Adjusted RD: 10%, 95% CI −2% to 23% **6 months:** CGM 11%, SMBG 9% Adjusted RD: 3%, 95% CI −9% to 14% Conclusion: There is no clear difference at 3 months; no difference between groups at 6 months.	⊕⊕◯◯ LOW
HbA1c %: Absolute reduction of ≥0.5% OR Relative reduction of ≥10% from baseline	3 and 6 months	1 (N=152 at 3 months; N= 158 at 6 months) Beck 2017[b]	Inconsistency (unknown) Imprecision (-1)	Absolute reduction **3 months:** CGM 61%, SMBG 38% Adjusted RD: 31%, 95% CI 5% to 57% **6 months:** CGM 56%, SMBG 37% Adjusted RD: 26%, 95% CI 0% to 50% Relative reduction **3 months:** CGM 44%, SMBG 26% Adjusted RD: 25%, 95% CI 3% to 46% **6 months:** CGM 40%, SMBG 24% Adjusted RD: 22%, 95% CI 0% to 42% Conclusion: Significantly greater proportion of CGM vs. SMBG subjects achieved both an absolute (≥0.5%) and a relative (≥10%) reduction in HbA1c at both timepoints. Confidence intervals were wide.	⊕⊕◯◯ LOW
HbA1c % (mean change from baseline)	3 months	3 (N=309) Beck 2017, Vigersky 2012, Yoo 2008	Imprecision (-1)	Pooled MD in change: -0.49%, 95% CI -0.71% to -0.26%, I^2 = 0% Conclusion: Clinically and statistically significant reduction with CGM versus SMBG	⊕⊕◯◯ MODERATE
	6 months	3 (N=308) Beck 2017[b], Tildesley 2013, Vigersky 2012,	RoB (-1) Imprecision (-1)	Pooled MD in change: -0.37% (95% CI -0.59% to -0.14%) Conclusion: Statistically significant reduction with CGM versus SMBG	⊕⊕◯◯ LOW
		Flash CGM 1 (N=224) Haak 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	CGM 8.37% (SD 0.83%), SMBG 8.34% (SD 1.14%) adjusted MD at follow-up: 0.03 (SE 0.114), p=0.822 Conclusion: No differences between FCGM and SMBG.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
	9.5 and 12 months	1 (N=100) Vigersky 2012	RoB (-1) Inconsistency (unknown) Imprecision (-1)	**9.5 months** MD in change -0.30, 95% CI -0.77 to 0.17 **12 months** MD in change -0.40, 95% CI -0.89 to 0.09 <u>Conclusion</u>: Small reduction at both timepoints with CGM versus SMBG; however the difference was not statistically significant and may not be clinically meaningful.	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (<50 mg/dl): minutes/day, % of time or % of SMBG readings/day in range **Flash CGM: minutes per day in range <55 mg/dl**	3 months	2 (N=242) Beck 2017[b], Ehrhardt 2011	Indirectness (-1) Imprecision (-1)	Minutes per day, median (IQR) (1 trial): CGM 0 (0-0) vs. SMBG 0 (0-3), p=ns % of time, median (IQR) (1 trial): CGM 0 (0-0) vs. SMBG 0 (0-0), p=ns % readings per day, mean (1 trial): CGM 1.9% vs. SMBG 2.7%, p=ns <u>Conclusion</u>: No statistically significant difference between groups.	⊕⊕◯◯ LOW
	6 months	1 (N=146) Beck 2017[b]	Inconsistency (unknown) Indirectness (-1)	<u>Minutes per day, median (IQR)</u>: CGM 0 (0-1) vs. SMBG 0 (0-5), p=ns <u>% of time, median (IQR)</u>: CGM 0 (0-0) vs. SMBG 0 (0-0.3), p=ns <u>Conclusion</u>: No statistically significant difference between groups.	⊕⊕◯◯ LOW
		Flash CGM 1 (N=224) Haak 2016	RoB (-1) Inconsistency (unknown) Indirectness (-1) Imprecision (-1)	<u>Minutes per day in range <55 mg/d:</u> CGM 11.4 (SD 22.2), SMBG 22.2 (SD 41.4) Adjusted MD at follow-up: -13.2 minutes (SE 4.1), p=0.0014 % difference CGM vs. SMBG: -53.1% <u>Events per day (<55 mg/dl), mean (SD)</u> CGM 0.14 (0.24), SMBG 0.24 (0.36); Difference in adjusted means: -0.12 (SE 0.037), p=0.002 % difference CGM vs. SMBG: -44.3% <u>Conclusion</u>: Statistically fewer minutes and episodes per day spent	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				in hypoglycemic range <55 mg/dl in the CGM vs. SMBG group.	
Hypoglycemia (<70 mg/dl): minutes/day, % of time or % of SMBG readings/day in range	3 months	2 (N=242) Beck 2017[b], Vigersky 2012	Indirectness (-1) Imprecision (-1)	Minutes per day, median (IQR) (1 trial): CGM 9 (1-25) vs. SMBG 11 (0-37), p=ns % of time, median (IQR): CGM 0.3 (0-1.5) vs. SMBG 0.6 (0-2.3), p=ns % readings per day, mean (1 trial): CGM 3.6% vs. SMBG 2.7%, p=ns Conclusion: No statistically significant difference between groups.	⊕⊕◯◯ LOW
	6 months	1 (N=146) Beck 2017[b]	Inconsistency (unknown) Indirectness (-1)	Minutes per day, median (IQR): CGM 4 (0-17) vs. SMBG 12 (0-34), p=ns % of time, median (IQR): CGM 0.3 (0-1.0) vs. SMBG 0.3 (0-2.3), p=ns Conclusion: No statistically significant difference between groups.	⊕⊕◯◯ LOW
		Flash CGM 1 (N=224) Haak 2016	RoB (-1) Inconsistency (unknown) Indirectness (-1) Imprecision (-1)	Minutes per day: CGM 35.4 (SD 49.2), SMBG 59.4 (SD 77.4) Difference in adjusted means at follow-up: -28.2 minutes (SE 8.0), p=0.0006 % difference CGM vs. SMBG: -43.1% Events per day (<70 mg/dl), mean (SD) CGM 0.38 (0.45), SMBG 0.53 (0.59); Difference in adjusted means: -0.16 (SE 0.065), p=0.016 % difference CGM vs. SMBG: -27.7% Conclusion: Statistically fewer minutes and episodes per day spent in hypoglycemic range <70 mg/dl in the CGM vs. SMBG group.	⊕◯◯◯ INSUFFICIENT
	12 months	1 (N=92) Vigersky 2012	RoB (-1) Inconsistency	% readings per day, mean: CGM 3.6% vs. SMBG 2.5%, p=ns	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
			(unknown) Indirectness (-1) Imprecision (-1)	Conclusion: No statistically significant difference between groups.	
Nocturnal Hypoglycemia (<50 and <70 mg/dl): % of time spent in range **Flash CGM: minutes per night (within 7 hours) in range <70 mg/dl <55 mg/dl**	3, 6 months	1 (N=151 at 3 months, N=146 at 6 months) Beck 2017[b]	Inconsistency (unknown) Indirectness (-1)	% of time, <50 mg/dl, median (IQR): 3 and 6 months: CGM 0 (0-0) vs. SMBG 0 (0-0), p=ns % of time, <70 mg/dl, median (IQR): 3 months: CGM 0.2 (0-1.8) vs. SMBG 0 (0-1.8), p=ns 6 months: CGM 0 (0-1.6) vs. SMBG 0 (0-2.9), p=ns Conclusion: No statistically significant difference between groups at 3 and 6 months for both measures.	⊕⊕◯◯ LOW
	6 months	Flash CGM 1 (N=224) Haak 2016	RoB (-1) Inconsistency (unknown) Indirectness (-1) Imprecision (-1)	Minutes per night <55 mg/dl: CGM 13.8 (SD 25.8), SMBG 30.6 (SD 43.2) Difference in adjusted means at follow-up: -17.4 minutes (SE 4.8), p=0.0001 % difference CGM vs. SMBG: -54.3% Events at night (<55 mg /dl) CGM 0.06 (0.13), SMBG 0.13 (0.21); Difference in adjusted means: -0.07 (SE 0.02), p=0.001 % difference CGM vs. SMBG: -53.0% Minutes per night <70 mg/dl: CGM 5.4 (SD 13.2), SMBG 11.4 (SD 24) Difference in adjusted means at follow-up: -7.2 minutes (SE 2.4), p=0.0032 % difference CGM vs. SMBG: -58.1% Events at night (<70 mg /dl) CGM 0.14 (0.420), SMBG 0.27 (0.33); Difference in adjusted means: -0.12 (SE 0.03), p=0.0003 % difference CGM vs. SMBG: -44.9% Conclusion: Statistically fewer minutes and episodes per night spent and in hypoglycemic ranges <55 and	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				<70 mg/dl in the CGM vs. SMBG group.	
Episodes of severe hypoglycemia	3-6 months	3 (N=264) Beck 2017[b], Tildesley 2013, Yoo 2008	Imprecision (-2)	No episodes of severe hypoglycemia, defined as an event requiring assistance from another person, were reported in either group in one trial (Beck 2017[b]) over 6 months. Two trials did not define severe hypoglycemia; one stated that no clinically symptomatic hypoglycemic events occurred over 3 months and the second trial reported that severe hypoglycemia in both the CGM and SMBG group was negligible with no serious events (data not provided, 6 month follow-up). Conclusions: Severe hypoglycemia is a rare event and trials were likely underpowered to detect differences between groups. No differences between groups in the frequency of severe hypoglycemic events.	⊕⊕◯◯ LOW
	6 months	Flash CGM 1 (N=224) Haak 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	Three CGM (2%) patients (3 events) and one SMBG (1%) patient (1 event) experienced a severe hypoglycemic event (an event requiring third party assistance). Conclusions: There is insufficient evidence to draw conclusions; study was likely underpowered to detect rare events.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

CGM versus SMBG efficacy results in women with preexisting type 1 diabetes during pregnancy

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
Gestational age (weeks)	up to 36 gestational weeks	2 (N=324) Feig 2017, Secher 2013	Imprecision (-1)	Pooled MD: -0.08 weeks, 95% CI -0.65 to 0.48, I^2 = 54% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕◯ MODERATE
Birthweight (grams)	up to 36 gestational weeks	2 (N=323) Feig 2017, Secher 2013	Imprecision (-1)	Pooled MD: 51.7 grams, 95% CI -132.22 to 235.67, I^2 = 36% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕◯ MODERATE
Miscarriage	up to 36 gestational weeks	2 (N=334) Feig 2017, Secher 2013	Imprecision (-1)	CGM 4.8%, SMBG 3.0% Pooled RD: 2.0%, 95% CI -2.0% to 6.0%, I^2 = 0% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕◯ MODERATE
Caesarean Section	up to 36 gestational weeks	2 (N=325) Feig 2017, Secher 2013	Imprecision (-1)	CGM 50.9%, SMBG 62.3% Pooled RD: -11.0%, 95% CI -21.0% to -1.0%, I^2 = 0% Conclusion: Statistically fewer caesarean sections in women using CGM vs. SMBG.	⊕⊕⊕◯ MODERATE
Preterm delivery	up to 36 gestational weeks	2 (N=325) Feig 2017, Secher 2013	Imprecision (-1)	CGM 31.3%, SMBG 34.0% Pooled RD: -2.0%, 95% CI -12.0% to 8.0%, I^2 = 0% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕◯ MODERATE
Preeclampsia	up to 36 gestational weeks	2 (N=325) Feig 2017, Secher 2013	Imprecision (-1)	CGM 8.6%, SMBG 14.2% Pooled RD: -5.0%, 95% CI -13.0% to 4.0%, I^2 = 34% Conclusion: No clear difference between CGM vs. SMBG.	⊕⊕⊕◯ MODERATE
Large for gestational age	up to 36 gestational weeks	2 (N=323) Feig 2017, Secher 2013	Inconsistency (-1) Imprecision (-1)	Point estimates differed between trials: MD 0.13, 95% CI -0.05, 0.30 (Secher) MD -0.16, 95% CI -0.29, -0.03 (Feig) Pooled RD: -2.0%, 95% CI -30.0% to 26.0%, I^2 = 85% Conclusion: Effect sizes for the two trials were in the opposite direction; one trial favored CGM the other did	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				not. No clear difference between CGM and SMBG. Pooled estimate did not reach significance; significant heterogeneity was noted.	
Severe Neonatal Hypoglycemia:2-hour plasma glucose <45 mg/dl and/or requiring IV glucose infusion	up to 36 gestational weeks	2 (N=317) Feig 2017, Secher 2013	Inconsistency (-1) Imprecision (-1)	CGM 15.3%, SMBG 23.8% Pooled RD: -7.0%, 95% CI -19.0% to 4.0%, I^2 = 46% Conclusion: No clear difference between CGM vs. SMBG in either outcomes. One trial showed a significant benefit for CGM while the other trial showed no significant difference between groups.	⊕⊕◯◯ LOW
Severe Maternal Hypoglycemia: episode requiring a third party intervention	up to 36 gestational weeks	2 (N=304) Feig 2017, Secher 2013	Inconsistency (unknown) Imprecision (-1)	1 trial, N=207 (Feig) CGM 10.7%, SMBG 11.5% (18 vs. 21 episodes, respectively) RD 1.0%, 95% CI -9.0% to 8.0% The second trial reported that 19 (16%) women experienced 59 severe hypoglycemic events, with no difference between the arms (data not provided). Conclusion: No statistical difference between groups.	⊕⊕◯◯ LOW
Neonatal hypoglycemia (2-hour plasma glucose <45 mg/dl)	up to 36 gestational weeks	1 (N=118) Secher 2013	Inconsistency (unknown) Imprecision (-1)	CGM 37%, SMBG 45% RD -8.2% (95% CI -25.9% to 9.6%) Conclusion: No clear difference between groups for neonatal hypoglycemia.	⊕⊕◯◯ LOW
Episodes of maternal hypoglycemic (CGM levels <63 mg/dl for at least 20 minutes; distinct events counted only if separated by ≥30 minutes)	34 weeks gestation	1 (N=154) Feig 2017	Inconsistency (unknown) Imprecision (-1)	Median (IQR) CGM 0.5 (0.3-0.8), SMBG 0.5 (0.3-0.8) Conclusion: No difference between CGM vs. SMBG.	⊕⊕◯◯ LOW
Major anomalies	up to36 gestational weeks	2 (N=334) Feig 2017, Secher 2013	Inconsistency (unknown) Imprecision (-2)	Congenital anomalies occurred in two (1.9%) and three (2.8%) infants in the CGM and SMBG groups, respectively, as reported by one trial (Feig), and consisted of aortic stenosis and	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				hypospadias grade 1 (CGM group) and hypoplastic right heart syndrome (termination of pregnancy), aberrant right subclavian artery, and bilateral hydronephrosis (SMBG group) The other trial reported that two infants (1.6%) had major congenital malformations: one ventricular septal defect combined with coarctation of the aorta and one congenitally corrected transposition of the great arteries; however the authors did not report to which group these women were randomized. Conclusion: Major anomalies are likely rare events. Insufficient evidence precludes firm conclusions.	
Stillbirth	34 gestations weeks	1 (N=211) Feig 2017	Inconsistency (unknown) Imprecision (-1)	CGM 0%, SMBG 0.9% RD -0.9%, 95% CI -2.8 to 0.9% Conclusion: No statistical difference between CGM vs. SMBG.	⊕⊕◯◯ LOW
Birth trauma (to include shoulder dystocia)	34 gestations weeks	1 (N=200) Feig 2017	Inconsistency (unknown) Imprecision (-1)	CGM 2%, SMBG 0% RD 2%, 95% CI not calculable, p=0.16 Conclusion: No difference between CGM vs. SMBG.	⊕⊕◯◯ LOW
Admission to neonatal intensive care unit (NICU) (>24 hours)	34 gestations weeks	1 (N=200) Feig 2017	Inconsistency (unknown) Imprecision (-1)	CGM 27%, SMBG 43% RD 16%, 95% CI -29% to -3% Conclusion: Statistically lower proportion of infants born to mothers in the CGM vs. SMBG group required admission to the NICU.	⊕⊕◯◯ LOW
Success (HbA1c ≤6.5%)	34 gestational weeks	1 (N=187) Feig 2017	Inconsistency (unknown) Imprecision (-1)	CGM 66%, SMBG 52% RD 14%, 95% CI 0.2 to 28.1, adjusted p=0.06 Conclusion: No clear difference between groups after controlling for baseline values and mode of insulin delivery.	⊕⊕◯◯ LOW
HbA1c %: mean change from baseline	3, 5.25 and 8.25 months	1 (N=119) Secher 2013	Inconsistency (unknown) Imprecision (-1)	**3 months:** MD 0.20, 95% CI -0.18 to 0.58 **5.25 months:** MD 0, 95% CI -0.38 to 0.38	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				8.25 months: MD 0.10, 95% CI -0.28 to 0.48 Conclusion: No statistical difference between CGM and SMBG at any timepoint.	
	6 to 6.75 months	2 (N=306) Feig 2017, Secher 2013	Imprecision (-1)	Pooled MD -0.09, 95% CI -0.30 to 0.13, I^2 = 30% Conclusion: No statistical difference between CGM and SMBG.	⊕⊕⊕◯ MODERATE
	8.5 to 9 months	2 (N=306) Feig 2017, Secher 2013	Imprecision (-1)	Pooled MD -0.15, 95% CI -0.32 to 0.01, I^2 = 0% Conclusion: No statistical difference between CGM and SMBG.	⊕⊕⊕◯ MODERATE
Hypoglycemia: % of SMBG values ≤70 mg/dl or % of time spent in the range <63 mg/dl	34 to 36 gestational weeks	2 (N=273) Feig 2017, Secher 2013	Inconsistency (unknown) Indirectness (-1) Imprecision (-1)	% of SMBG values ≤70 mg/dl (1 trial, Secher) Median 14% (range 0% to 25%) for both CGM and SMBG groups, p=0.96; authors report that the women had a median of 4 (range 0-14) mild hypoglycemic events per week, with no difference between the groups (data not provided), but do not report events separately for type 1 and type 2 diabetes % of time <63 mg/dl, median (IQR) (1 trial, Feig) CGM 3% (1%-6%), SMBG 4% (2%–8%), p=0.10 Conclusion: No statistical difference between groups.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

CGM versus SMBG efficacy results in women with preexisting type 2 diabetes during pregnancy

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
Gestational age and birth weight	up to 36 gestational weeks	1 (N=31) Secher 2013	Inconsistency (unknown) Imprecision (-2)	CGM vs. SMBG, respectively (median, range): • *Gestational age*: 262 (206-280) vs. 267 (259-277) days, p=0.17 • *Birth weight*: 3,371 (1,070-4,260) vs. 3,343 (2,773-3,818) grams, p=0.70 Conclusion: No differences between groups. Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Proportion of infants large for gestational age	up to 36 gestational weeks	1 (N=31) Secher 2013	Inconsistency (unknown) Imprecision (-2)	CGM 25% vs. SMBG 29% RD -1.7%, 95% CI -32.5% to 29.2% Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Neonatal hypoglycemia (2-hour plasma glucose <45 mg/dl) and **Severe Neonatal hypoglycemia** (2-hour plasma glucose <45 mg/dl treated with IV glucose infusion)	up to 36 gestational weeks	1 (N=28) Secher 2013	Inconsistency (unknown) Imprecision (-2)	Neonatal hypoglycemia: CGM 31%, SMBG 14% RD 17.4%, 95% CI -13.0% to 47.9% Severe neonatal hypoglycemia: CGM 0%, SMBG 0% Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Miscarriage	up to 36 gestational weeks	1 (N=31) Secher 2013	Inconsistency (unknown) Imprecision (-2)	CGM 0% vs. SMBG 7% RD -6.7% (95% CI -19.3% to 6.0%) Conclusion: One woman miscarried in the SMBG group compared with no women in the CGM group; insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Perinatal mortality	up to 36 gestational weeks	1 (N=31) Secher 2013	Inconsistency (unknown) Imprecision (-2)	One case (3.2%, N=31) shortly after delivery due to severe shoulder dystocia. The authors did not report to which group the woman was randomized. Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Caesarean section rates	up to 36 gestational weeks	1 (N=31) Secher 2013	Inconsistency (unknown) Imprecision	CGM 50% vs. SMBG 40% RD -10.0%, 95% CI -24.9% to 44.9%	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
			(-2)	Conclusion: Insufficient evidence precludes drawing firm conclusions.	
HbA1c % (Median)	8 to 36 gestational weeks	1 (N=30) Secher 2013	Inconsistency (unknown) Imprecision (-2)	CGM vs. SMBG, respectively (median, range): • *8 weeks*: 6.4 (5.3-8.1 vs. 6.5 (5.3-9.0), p=0.56 • *12 weeks*: 6.2 (5.6-7.8) vs. 6.2 (5.1-7.7), 0.90 • *21 weeks*: 5.7 (5.2-6.9) vs. 5.6 (4.6-6.3), p=0.24 • *27 weeks*: 5.8 (5.0-7.7) vs. 5.7 (4.8-6.6), p=0.28 • *33 weeks*: 6.0 (5.1-7.0) vs. 5.9 (5.2-6.8), p=0.44 • *36 weeks*: 6.0 (5.1-6.5) vs. 5.9 (5.2-6.7), p=0.31 Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (% of SMBG values ≤70 mg/dl throughout pregnancy)	up to 36 gestational weeks	1 (N=30) Secher 2013	Inconsistency (unknown) Indirectness (-1) Imprecision (-2)	CGM: median 5% (range 0%-19%) SMBG: median 4% (range 0%-15%) p=0.79 Authors report that the women had a median of 4 (range 0-14) mild hypoglycemic events per week, with no difference between the groups (data not provided), but do not report events separately for type 1 and type 2 diabetes Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕◯◯◯ INSUFFICIENT
Severe hypoglycemia (requiring second party intervention)	up to 36 gestational weeks	1 (N=30) Secher 2013	Inconsistency (unknown) Imprecision (-2)	5 (17%) women experienced 15 severe hypoglycemic events, with no difference between the arms (data not provided). Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
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4. Indirect, intermediate or surrogate outcomes may be downgraded.

CGM versus SMBG efficacy results in women with gestational diabetes

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
Gestational age and birth weight	36 gestational weeks	1 (N=106) Wei 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	CGM vs. SMBG, respectively: • *Gestational age*: 37.5 ± 1.3 vs. 37.4 ± 0.1 weeks, p=0.92 • *Birth weight*: 3276 ± 520 versus 3451 ± 514 grams, p=0.08 Conclusion: No statistical difference between groups, though infants born to mothers in the CGM vs. SMBG group tended to weigh less.	⊕○○○ INSUFFICIENT
Proportion of infants with macrosomia or large for gestational age	36 gestational weeks	1 (N=106) Wei 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	• *Macrosomia (birth weight >4000 g)*: CGM 8% vs. SMBG 13% RD -4.9%, 95% CI -16.4% to 6.6% • *Large for gestational age (≥90th percentile)*: CGM 35% vs. SMBG 53% RD -17.4%, 95% CI -36.0% to 1.2% • *Extremely large for gestational age (≥97.7th percentile)*: CGM 18% vs. SMBG 31% RD -13.3%, 95% CI -29.3% to 2.8% Conclusion: Infants born to women in the CGM vs. the SMBG group tended to be somewhat smaller, however there were no significant differences between groups on any measure.	⊕○○○ INSUFFICIENT
Neonatal hypoglycemia	36 gestational weeks	1 (N=106) Wei 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	CGM 8% vs. SMBG 13% RD -4.9%, 95% CI -16.4% to 6.6% Conclusion: No statistical difference between groups.	⊕○○○ INSUFFICIENT
Perinatal mortality	36 gestational weeks	1 (N=106) Wei 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	No perinatal deaths were observed in either the CGM or SMBG group. Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Caesarean section rates	36 gestational weeks	1 (N=106) Wei 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	CGM 60% vs. SMBG 69% RD -8.3%, 95% CI -26.4% to 9.8% Conclusion: No statistical difference between groups.	⊕○○○ INSUFFICIENT
HbA1c % (mean	32-36 gestational weeks	1 (N=106) Wei 2016	RoB (-1) Inconsistency	MD -1.0%, 95% CI -0.24% to 0.04%	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	Reason for downgrading	Conclusion	Quality
change from baseline)			(unknown) Imprecision (-1)	Conclusion: CGM group showed slightly lower levels vs. the SMBG group, but the difference between groups was not statistically significant.	

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Safety and Adverse Events Results for CGM

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
Adverse events leading to discontinuation	3-6.5 months	8 (N=25 to 142) Battelino 2011, Deiss 2006, Hermanides 2011, O'Connell 2009, Tildesley 2013, Wei 2016, Lind 2017, van Beers 2016 2 observational (N=83 to 1714) 1 prospective cohort (Rachmiel 2015), 1 retrospective registry (Wong 2014)	Inconsistency (-1) Imprecision (-1)	Frequency in CGM arm across all RCTs was 0% to 24%. Older devices (6 trials): frequency 2% to 24%; the most common reasons for discontinuation included: • Difficulty operating the device and/or sensor (3% to 8%, 3 RCTs) • Alarms too frequent (6% in 2 RCTs) • Treatment discomfort or inconvenience; (20%, 1 small RCT, n=25) Newer devices (2 trials, N=52 to 142; Lind, van Beers): frequency, 1% to 4%; reasons for discontinuation were: • Allergic reaction to sensor (1%) • Could not upload CGM data (4%) Observational studies: Frequency much higher (61% and 44%) with similar reasons for stopping CGM use as were cited in the RCTs; however both studies were considered high risk of bias	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				Conclusion: Discontinuation due to device-related adverse events was not uncommon in included studies. Most patients stopped CGM use due to difficulty operating the device or frequency of alarms (bothersome).	
	6 months	Flash CGM 2 (N=269) Bolinder 2016, Haak 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	Frequency 2% to 5% across trials and included itching, rash, erythema, redness and weeping at the sensor insertion site; some events were unclear/not specified. Conclusion: Site-related AE discontinuation was not common; Reporting of adverse events was unclear.	⊕◯◯◯ INSUFFICIENT
Serious device related adverse events (proportion with ≥1 event)	6-12 months	11 (N=14 to 244) Bergenstal 2010, Hermanides 2011, Hirsch 2008, Hommel 2014, JDRF 2008, JDRF 2009, Lind 2017, Maurus 2012, Tumminia 2015, Feig 2017, van Beers 2016	Inconsistency (-1) Imprecision (-1)	Frequency in CGM arm across all trials was 0% to 7%. Older CGM devices (9 trials): 0% to 7% and included: • Hospitalization for ketoacidosis (2% to 7%, 2 trials); *one case, 2% (1/44), was caused by pump failure.* • Serious skin reactions (0% to 6%, 2 trials) • Diabetes-related hospitalization (3%, 1 trial) • Insertion site infections resulting in cellulitis or skin abscess (1% each, 3 trials) • Serious device or study related adverse events not otherwise specified (0%, 2 trials) Excluding the trial with a very small sample size (n=14), the rate of serious device related adverse events was 0%-3%. Newer devices (2 trials, N=52 to 142, Lind, van Beers): % to 1%; the only serious device-related adverse event (as reported by authors) was Retinal detachment (1%) Conclusion: Serious device related adverse events (as reported by	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				authors) were relatively rare across the trials. Sample size may be too small to detect rare outcomes.	
	6 months	Flash CGM 2 (N=269) Bolinder 2016, Haak 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	Frequency 1% to 3% included allergic reaction at sensor site, necrosis at sensor site, infection at sensor site and, rash, erythema, pain, and itching, Conclusion: Serious AEs appear to be rare, however severity is not defined and reporting of adverse events was unclear.	⊕◯◯◯ INSUFFICIENT
Non serious device-related adverse events (proportion with ≥1 event)	3 to 8.5 months	7 (N=25 to 157) Hermanides 2011, Lind 2017, New 2015, Yoo 2008, Tildesley 2013, Wei 2016, Feig 2017 1 prospective cohort (n=83) Rachmiel 2015	RoB (-1) Imprecision (-1)	Frequency: 0% to 45% across all trials. Skin-related problems (e.g., erythema, inflammation, rash/allergic reaction, mild infection) at the sensor or insulin infusion site accounted for most of the events. Excluding the trial in women with preexisting type 1 DM during pregnancy (Feig) which reported 45% with skin changes (e.g. erythema, edema, scabbing, dry skin, hypo- and hyperpigmentation, other) the range across trials was 0% to 24%. Newer device (N= 142, Lind): 3% of patients experience skin-related problems, including allergic reaction to sensor, inflammation, itching, and rash at application site. The cohort study also reported that local skin reaction/irritation was common (36% of CGM patients) <u>Conclusion</u>: Non-serious device related adverse events, especially skin-related problems, are common with CGM use.	⊕⊕◯◯ LOW
	6 months	Flash CGM 2 (N=269) Bolinder 2016, Haak 2016	RoB (-1) Inconsistency (unknown) Imprecision (-1)	Reported frequency of *events* 4% to 8% included allergic reaction at sensor site, rash, erythema, pain, and itching, edema, infection at sensor site.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
				Trials also reported "expected sensor-insertion site *symptoms*" (not considered AEs by the authors), which occurred in 28% and 40% of subjects, and consisted of events similar to those reported as "non-serious device-related" events but provide no definitions or criteria to distinguish AE and symptom; it is unclear how these two outcomes differ and if there is overlap between them. Conclusion: Definitions of adverse events/distinction between events and symptoms was unclear, making it challenging to draw definitive conclusions	
Technical or mechanical issues	3 months	4 (N=27 to 157) Langeland 2012, Lind 2017, O'Connell 2009, Feig 2017	RoB (-1) Imprecision (-1)	Frequency in CGM arms (3 trials):1% to 16%; issues, in 1 trial each, included: • Technical problems with sensor leading to loss of all glucose readings (15%) • Mechanical problems, not further specified (16%) • "Device issue" (1%) (newer CGM device; Lind) Women with preexisting T1DM during pregnancy (1 RCT, n=103 CGM), older CGM device (Feig): • 81% reported issues related to transmitter/receiver connection, various sensor problems; others (not specified) • 78% did not use the device (alarms too frequent, inaccurate readings, too difficult to operate, sensor errors, calibration issues, other) **Conclusion:** Definitions and reporting of technical or mechanical issues varied and were not well reported across trials	⨁⨁◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)

2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Differential Efficacy and Harms for CGM versus SMBG in adults with type 1 or type 2 diabetes

Exposures	Outcome	Follow-up	RCTs	Reasons for downgrading	Conclusion	Quality
Baseline HbA1c; Age; Percent of CGM time <70 mg/dl; SMBG frequency; Education; Hypoglycemia Unawareness Score; Diabetes Numeracy Score; Hypoglycemia Fear Total Score; Type of clinical site (T1DM only)	Change from baseline in HbA1c %	6 mos.	**T1DM** 1 RCT (N=155) (Beck 2017)[a] **T2DM** 1 RCT (N=152) (Beck 2017[b])	Inconsistency (unknown) Indirectness (-1) Imprecision (-1) HTE-related (-1)	**T1DM** No factors modified effect. **T2DM** Baseline Hypoglycemia Unawareness Survey scores: greater reduction in mean HbA1c % levels in subjects with **reduced awareness or uncertainty (score ≥3)**, vs. higher awareness (score ≤2), following **CGM** but not SMBG (interaction p=0.031). No other factors modified **Conclusion:** Insufficient evidence precludes drawing firm conclusions.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Comparisons of an intervention to placebo or usual care is considered indirect.

The following apply specifically to heterogeneity of treatment effect (HTE):

5. Subgroup analysis not preplanned or unknown
6. Statistical test for homogeneity or interaction not performed

Cost-effectiveness of CGM versus SMBG in adults with type 1 diabetes

Type 1 Studies:	Chaugule 2017 Canada QHES 86/100	Huang 2010 U.S. QHES 85/100	McQueen 2011 U.S QUES 93/100	Roze 2014 Sweden QHES 93/100
Population	Adult (mean 46 y.o.) Baseline HbA1c = 8.6% Type I Diabetes 53% Male MDI	Two A1c cohorts : Adults (mean 43 y.o. ,25-73), Baseline A1c = 7.6 (SMBG) and 7.1% (CGM): 57% Female; A 1c <7.0% (age 31y.o., 8-65) MDI and CSII	Adults (mean 40 y.o.) Baseline HbA1c = 7.6% 20 yrs. since diagnosis MDI and CSII	Adult (mean 27 y .o.) Baseline A1c = 8.6% 54.5% Female Assumed 13 yrs. since diagnosis CSII
	DIAMOND Trial	JDRF, DCCT, publications	C.D.C. Cost-Effectiveness Group, CGM, relied on professional expertise DCCT, publications	IMS CORE Diabetes Model, DCCT, publications
Time horizon	50 years	Lifetime	33 years	70 years
ICER	$43,926/ QALY	$98,679 / QALY	$45,033 / QALY	$57,433 / QALY
Sensitivity analyses $/QALY Range/Drivers	$42,552 to $84, 972 % A1c reduction; 50% decrease in hypoglycemia disutility	$70,000 to $701,397 ↓CGM cost/day to $9.89; restrict benefit to lowering glucose	DM utility -no complications↓, ↑ by 50%; $300,000 ($30,000); Annual CHD costs ↓, ↑ by 50%, $86,000 ($12,000); 48% Monte Carlo simulations < US$50,000; 70% of simulations < US$100,000/QALY	$43,751 to $92,759 2.1 SMBG/day, Δ baseline A1c to 7.2%; ↑ rate of severe hypoglycemic events $46,349 /QALY.
Author's Conclusion	At WTP threshold of $50,000 CGM robustly, cost effective vs. SMBG	Wide uncertainty (CI included CGM dominating and being dominated by SMBG); Immediate quality-of-life effect of CGM responsible majority of projected lifetime benefits	CGM was found to be cost effective in more circumstances than not, given a WTP of $100,000.	CGM is a cost–effective option in the treatment of Type 1 diabetes in Sweden
Limitations	• Canadian societal perspective stated; only direct costs reported • Sensitivity analyses related to long term impact of microvascular	• CV complications From T2DM CV models. • High baseline utilities placed a ceiling on the potential quality-of-life benefit of CGM • Unclear if use of DCCT models for microvascular	• Some costs were extrapolated from studies that include all age groups. • RCT data provide information up to 12 months; sustainability of improved A1C unclear	• Swedish societal perspective • Limited acknowledgment of modeling, study limitations • Model assumes lifetime horizon; RCT data provide information up to 12 months.

Type 1 Studies:	Chaugule 2017 Canada QHES 86/100	Huang 2010 U.S. QHES 85/100	McQueen 2011 U.S QUES 93/100	Roze 2014 Sweden QHES 93/100
	and macrovascular complications not presented • Assumes lifetime horizon; RCT data for up to 12 months. Change in A1C based on DIAMOND trial; Unclear if 1% change with CGM use over lifetime is sustainable. • Industry funded	complications and T1DM models for cardiovascular complications reflect current care	• Substantial variation in ICER estimates based on sensitivity analysis/modeling of diabetes complications based on probability evaluations from different populations	• Industry ties

Cost-effectiveness of CGM versus SMBG in adults with type 2 diabetes

Type 2 Studies:	Fonda 2016[20] U.S. QHES 75/100
Population Adults	57.8 y.o.; T2DM least 3 months. Not taking prandial insulin. Initial A1C of between 7% and 12% ; MDI and CSII
Perspective	Third-party payer (direct costs only)
Time horizon	Lifetime
Clinical data	Risk adjustments from UKPDS, DCCT Framingham Heart Study, literature CORE Diabetes Model
ICER	$8,898 / QALY
SA	Probabilistic cost-effectiveness analysis: likelihood CGM CE 70% at the willingness-to-pay threshold of $100,000/QALY.
Author's Conclusion	CGM offers a cost-effective alternative to populations matching that the trial specifically: short-term, intermittent use in people with type 2 diabetes.
Limitations	• Small sample size of trial (n = 100) to estimate effectiveness parameters. • Limited sensitivity analyses presented; results of one-way SA not discussed • Used older CGM device that has since been update. • Life-time horizon used; Few RCT data past on long-term CGM use in type 2 DM. • Unclear if use of DCCT, USPKD and Framingham data for complications reflect current care • Industry funding

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1. Appraisal

1.1 Background and Rationale

Diabetes mellitus (DM), or diabetes, is a serious metabolic disease characterized by chronic elevation of blood glucose (i.e., hyperglycemia) resulting from defects in insulin secretion, insulin action, or both. No definitive cure is known at this time. Diabetes is generally categorized into three major types based on etiology: Type 1 diabetes (T1DM) (formerly called juvenile diabetes or insulin-dependent diabetes mellitus [IDDM]), Type 2 diabetes (T2DM) (formerly called adult onset diabetes mellitus [AODM] or non-insulin dependent diabetes [NIDDM]), and gestational diabetes mellitus (GDM).

Diabetes is a leading cause of morbidity and mortality and is associated with substantial healthcare and societal costs. An estimated 29.9 million Americans (9.3% of the population) had diabetes in 2015 and, by 2050, the prevalence of diabetes in the U.S. adult population is projected to increase to between 21% and 33%.[24] T2DM is the most common form and accounts for 90% to 95% of all diabetes. Serious complications related to diabetes include diabetic ketoacidosis (DKA), which occurs when fatty acids called ketones build-up in the bloodstream, and hyperosmolar hyperglycemic nonketotic syndrome (HHNS) characterized by extremely high blood glucose levels without the presence of ketones, as well as longer term morbidity due to microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., heart disease, stroke) complications; other diabetes related complications include increased risk of infections, cancer and other autoimmune disorders including celiac sprue, thyroid disease, rheumatoid arthritis, and vitiligo.

For T2DM, oral, non-insulin mediations are generally used initially in combination with lifestyle management education to attain glycemic control. Insulin therapy is the only effective therapy for persons with T1DM and is used for T2DM who cannot produce sufficient insulin[8,20] and pregnant women with any type with elevated glucose.[101] Not all those with T2DM will require insulin. The insulin dose depends on body weight, age, food intake, and activity. Intensive insulin therapy, a term used to describe tight management of blood glucose levels, has been shown to reduce the risk of long-term diabetic complications by lowering average blood sugar levels, but also increases the risk of hypoglycemia, which can result in serious morbidity and even death, and causes fear of hypoglycemia which is a major barrier to optimal glucose control. Insulin may be delivered via multiple daily injections or via continuous subcutaneous insulin infusion using an insulin pump. Greater fluctuation in blood glucose levels may be seen in patients requiring insulin and more attention to monitoring blood glucose levels may be needed.

Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) are two techniques that persons with diabetes can use at home to help them maintain glucose levels within a safe range. Real-time continuous glucose monitoring (CGM) is advanced glucose monitoring technology that continuously measures interstitial glucose levels, displays the current glucose level as well as the direction and rate of change, allows for evaluation of glycemic variability and uses alarms and alerts to inform patients when glucose levels exceed or fall below specified thresholds.[25] Conventional fingerstick self-monitoring of blood glucose (SMBG), sometimes called intermittent monitoring, is a technique for testing blood glucose using a portable glucose meter designed for home use. SMBG provides an instantaneous reading of current blood glucose levels at single points in time, but cannot indicate

whether the glucose level is on its way up or down. CGMs were designed to aid in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long term therapy adjustments, which may minimize these excursions. With the exception of three FDA-approved devices (T:slim X2 Insulin Pump with Dexcom G5 Mobile CGM, Dexcom G5 Mobile CGM System, and FreeStyle Flash Libre CGM System), CGMs are intended to complement, not replace, information obtained from a standard home glucose monitoring device; they are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. It should be noted, however, that technological advances of CGM sensors and algorithms over recent years has made the accuracy of CGM devices more comparable to that of SMBG. CGMs can be used as stand-alone devices or in conjunction with compatible insulin pumps. When CMG is used together with an insulin pump, it may be referred to as sensor augmented pump therapy (SAP). In the past 5 years, improvements in CGM technology resulting in better accuracy and performance have contributed to more widespread use of these devices.

Policy Context

This topic was originally reviewed in 2011. It is proposed for re-review based on new evidence and newly expanded indications for continuous glucose monitoring (CGM). New evidence and indications are identified that support re-reviewing the evidence for continuous glucose monitoring.

Objectives

The first aim of this report is to update the 2011 HTA on glucose monitoring in children and adolescents by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of continuous glucose monitoring in persons under 18 years old with insulin requiring diabetes mellitus. The second aim is to systematically review, critically appraise and analyze research evidence on the safety and efficacy continuous glucose monitoring in persons with type 1 or type 2 diabetes (regardless of insulin requirement), including pregnant women with pre-existing or gestational diabetes. SMBG as a stand-alone means of monitoring blood glucose will not be included as an intervention. This report does not include evaluation of insulin delivery systems (automated or other).

1.2 Key Questions

In persons with diabetes mellitus (DM):

1. What is the evidence of efficacy and effectiveness of continuous monitoring?

2. What is the evidence of the safety of continuous glucose monitoring?

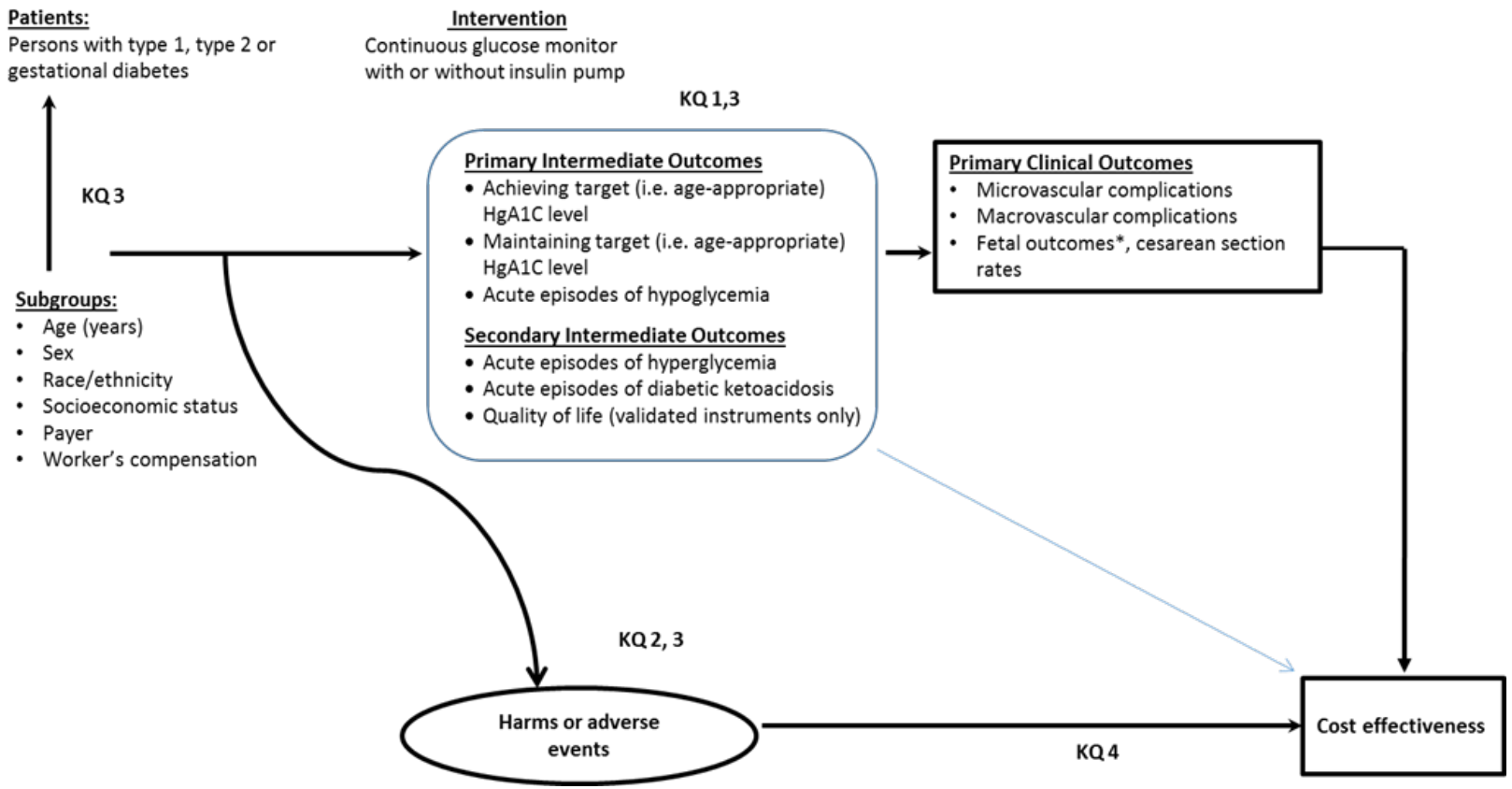
3. What is the evidence that glucose monitoring has differential efficacy or safety issues in subpopulations?

4. What is the evidence of cost-effectiveness of continuous glucose monitoring?

Inclusion and exclusion criteria are summarized as follows and are detailed in the full report. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Persons with diabetes mellitus, including those with type 1 and type 2, and pregnant women with pre-existing diabetes or gestational diabetes
- **Interventions:** FDA-approved real-time continuous glucose monitoring devices and FDA-approved combination devices integrating real-time continuous glucose monitoring with insulin pump/infusion (including sensor augmented insulin pumps)
- **Comparators:** Self-monitoring using convention blood glucose meters, attention control, blinded or sham CGM and usual care. Comparisons of one CGM device with another with another will be excluded
- **Outcomes:** Primary clinical outcomes are 1) microvascular complications, 2) macrovascular complications, 3) fetal outcomes, cesarean section rates. Primary intermediate outcomes are 1) achieving target (i.e. age-appropriate) HgA1C level, 2) maintaining target (i.e. age-appropriate) HgA1C level, 3) acute episodes of hypoglycemia. Safety outcomes are 1) mortality, 2) morbidity from glucose meters or monitors. Economic outcomes are cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcomes.
- **Studies:** Focus is on high quality comparative studies (e.g. randomized trials) for Key Questions 1-3; observational studies with long term clinical outcomes or safety will also be considered for Key Questions 1-3. Full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be sought for Key Question 4; studies using modeling may be used to determine cost-effectiveness over the full duration of glucose monitoring, which is a lifetime.

Figure 1. Analytic framework



*Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit, stillbirth, and neonatal and perinatal mortality

1.3 Outcomes Assessed

Ideally, direct evidence over a long term of follow-up from randomized controlled trials that evaluate the impact of SMBG and CGM on diabetes-related morbidity and mortality would be available. Hemoglobin A1C is considered an intermediate (surrogate) outcome and, in the absence of such trials, provides the best available evidence as it is considered a predictor of diabetes complications.

The primary outcomes of interest for this report are listed below; these were designated as primary outcomes based on clinical expert input:

- Microvascular complications (e.g., retinopathy, nephropathy, neuropathy)
- Macrovascular complications (e.g., ischemic heart disease, peripheral vascular disease, cerebrovascular disease)
- Fetal outcomes (e.g., gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit, stillbirth, and mortality)
- Cesarean section rates

Primary intermediate outcomes of interest include:

- Achieving target (i.e. age-appropriate) HbA1c level
- Maintaining target (i.e. age-appropriate) HbA1c level
- Acute episodes of hypoglycemia

Consistent with the previous report we used a change of ≥0.5% in HbA1c to denote a clinically significant improvement/difference. Some trials also suggest that a cut-off of ≥0.3% may be clinically relevant. [91]

Secondary intermediate outcomes of interest include:

- Acute episodes of hyperglycemia
- Acute episodes of diabetic ketoacidosis
- Quality of life (validated instruments only); measures reported in the included trials are as follows:

Outcome	Outcome Scale, Direction
World Health Organization Well-Being Index (WHO-5)	0–100, higher score indicates greater well-being
EQ-5D-5L	-0.594 to 1.0, higher score indicates better state of health
Diabetes Distress Scale (DDS)	0–6, higher score indicates higher distress
Hypoglycemia Fear Survey HFS-II	0–132, higher score indicates higher fear Worry subscale: 0–60, higher score indicating higher worry
Hypoglycemia Confidence Scale (HCS)	1–4, higher score indicates higher confidence
Clarke Hypoglycemia Unawareness Questionnaire	0–7, higher score indicates higher unawareness
KIDSCREEN-27	0–100 (norm based), higher score indicates better functioning
Problem Areas in Diabetes (PAID) and PAID Parent-reported (PAID-P)	0–100, higher score indicates more problems
Pediatric Quality of Life (PedsQL)	0–100, higher score indicates better quality of life

	Psychosocial and Physical Health Summary subscales: 0–100, higher score indicates higher functioning
Diabetes Treatment Satisfaction Questionnaire (DTSQ)	0–36, higher score indicates higher satisfaction
Short Form (SF)-36, SF-12, SF-8	0–100, higher score indicates better quality of life PCS and MCS subscales: 0–100, higher score indicating higher quality of life
Hypoglycemia Fear Survey (HFS)	0–100, higher score indicates greater fear Worry and Avoidant Behavior subscales: 0–100, higher score indicates greater worry/avoidance
CGM Satisfaction Survey (CGM-SAT)	1–5, higher score indicates greater satisfaction Benefit and Lack of hassle subscales: 1-5, higher score indicates greater benefits or fewer hassles

For all outcomes, our focus was on measures of "success" when reported (proportion of patients meeting a pre-specified threshold of success for treatment; definition may vary across studies). Common success measures reported by the included trials include an absolute reduction of ≥0.5% in HbA1c from baseline, a relative reduction of ≥10% in HbA1c from baseline, and HbA1c <7.0% at follow-up.

Strength of evidence was assessed for the primary clinical and primary intermediate outcomes only.

1.4 Washington State Utilization and Cost Data

Populations

The *Continuous Glucose Monitoring (CGM)* analysis includes member utilization and cost data from the following agencies: PEBB/UMP (Public Employees Benefit Board Uniform Medical Plan); PEBB Medicare; and the HCA Medicaid (formerly Fee-for-Service) and the Managed Care (MCO) Medicaid program. There were no claims from the Department of Labor and Industries (LNI) workers' compensation plan

The analysis period was four (4) calendar years, 2013 - 2016. Primary population inclusion criteria included having a diagnosis of either Type I or Type II diabetes AND experiencing at least one of the CPT/HCPCS codes from Table I. Denied claims were excluded from the analysis.

Methods

CGM RR utilization was calculated based on an individual having: 1) a diagnosis of either Type I or Type II diabetes; 2) experiencing at least on paid, provider Evaluation & Management code annually; and having a paid claim for one of the CPT codes from Table I. Data evaluation included examining average utilization and costs by member compared to patients with diabetes and without incurred CGM claims.

Table I: Continuous Glucose Monitoring CPT Codes and Descriptions

CPT	CPT Description
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
A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with interstitial continuous glucose monitoring system, one unit = 1 day supply
A9277	Transmitter; external, for use with interstitial continuous glucose monitoring system
A9278	Receiver (monitor); external, for use with interstitial continuous glucose monitoring system
S1030	Continuous noninvasive glucose monitoring device, purchase (for physician interpretation of data, use CPT code)
S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (for physician interpretation of data, use CPT code.

Table II: CGM-Type Coding Not Used

CPT	Status	CPT Description
0446T	Eff Jan 2017	Creation of subcutaneous pocket with insertion of implantable interstitial glucose sensor, including system activation and patient training Eff Jan 2017
0447T	Eff Jan 2017	Removal of Implantable interstitial glucose sensor from subcutaneous pocket via incision Eff Jan 2017
0448T	Eff Jan 2017	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation Eff Jan 2017
K0553	Eff July 2017	Supply allowance for therapeutic continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 Unit Of Service Eff July 1, 2017
K0554	Eff July 2017	Receiver (monitor), dedicated, for use with therapeutic glucose continuous monitor system Eff July 1 2017
S9145	Nonspecific for CGM	Insulin pump initiation, instruction in initial use of pump (pump not included)
S1034	Artificial Pancreas	Artificial pancreas device system (e.g., low glucose suspend (lgs) feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
S1035	Artificial Pancreas	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
S1036	Artificial Pancreas	Transmitter; External, For Use With Artificial Pancreas Device System
S1037	Artificial Pancreas	Receiver (Monitor); External, For Use With Artificial Pancreas Device System
A9274	Nonspecific for CGM	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories
A9275	Nonspecific for CGM	Home glucose disposable monitor, includes test strips
E0607	Nonspecific for CGM	Home blood glucose monitor
E0784	Nonspecific for CGM	External ambulatory infusion pump, insulin

Table III: Definitions for Utilization and Cost

Unique Patients	Non-duplicated patient by year, reported by agency

2013 – 2016 Data Tables
Continuous Glucose Monitoring (CGM) Re-Review
NOTE: LNI did not have claims for CGM

2013 -2016 PEBB/ UMP
Paid Dollars by Year for CGM and Related Items (CPT/HCPCS)

	Unique Patients	256	332	456	618	1,113
Proc Code HCPCS	**Proc Long Desc - HCPCS**	**2013**	**2014**	**2015**	**2016**	**TOTAL**
95250	GLUCOSE ONITORING, 72 HRS, CONT REC & STORAGE, GL	$15,210	$16,637	$17,259	$25,892	**$74,998**
95251	AMBULATORY CONTINUOUS GLUCOSE MONITORING OF INTESTINAL FLUID, INTERPRETATION/RPT	$2,730	$5,649	$8,136	$13,212	**$29,727**
A9276	SENSOR; INVASIVE (E.G. SUBCUTANEOUS), DISPOSABLE, FOR USE WITH INTERSTITIAL	$183,610	$351,509	$570,434	$824,323	**$1,929,876**
A9277	TRANSMITTER; EXTERNAL, FOR USE WITH INTERSTITIAL CONTINUOUS GLUCOSE MONITORING	$46,396	$78,605	$122,773	$185,850	**$433,624**
A9278	RECEIVER (MONITOR); EXTERNAL, FOR USE WITH INTERSTITIAL CONTINUOUS GLUCOSE	$19,337	$22,884	$37,796	$57,752	**$137,769**
	Grand Total	$267,283	$475,284	$756,398	$1,107,029	**$2,605,994**

2013 -2016 PEBB/ UMP
Count of CGM Related Units and Average Paid Dollars/Code
CGM and Related Items (CPT/HCPCS)

Proc Code	Proc Long Desc - HCPCS	2013	2013 Avg Pd$	2014	2014 Avg Pd $	2015	2015 Avg Pd $	2016	2016 Avg Pd $	Total
95250	CGM	77	$198	94	$177	103	$168	141	$184	**957**
95251	AMB CGM	55	$50	110	$51	153	$53	249	$53	**721**
A9276	SENSOR	327	$561	572	$615	865	$659	1,155	$714	**4,754**
A9277	TRANSMIT-TER	107	$434	196	$401	291	$422	396	$469	**2,247**
A9278	RECEIVER	49	$395	67	$342	106	$357	144	$401	**1,459**
	Grand Total	**615**	$435	**1,039**	$457	**1,518**	$498	**2,085**	$531	**6,647**

2013 -2016 Medicare/PEBB
Paid Dollars by Year for CGM and Related Items (CPT/HCPCS)
NOTE: PEBB pays secondary to Medicare

Proc Code	Proc Long Desc - HCPCS	2013	2014	2015	2016	TOTAL
95250	GLUCOSE MONITORING, 72 HRS	$2,519	$1,413	$2,301	$3,781	$10,014
95251	AMBULATORY CGM	$256	$421	$543	$994	$2,214
A9276	SENSOR	$45,064	$37,087	$57,921	$84,121	$224,193
A9277	TRANSMITTER	$4,542	$9,541	$13,640	$24,839	$52,562
A9278	RECEIVER	$2,980	$5,363	$5,355	$6,385	$20,083
	Grand Total	$55,361	$53,825	$79,760	$120,120	$309,066

2013 -2016 Medicare/PEBB
Count of Service Units Related to CGM (CPT/HCPCS)
NOTE: PEBB pays secondary to Medicare

Proc Code - HCPCS	Proc Long Desc - HCPCS	2013	2014	2015	2016	TOTAL
95250	GLUCOSE MONITORING, 72 Hr	57	54	64	124	299
95251	AMBULATORY CGM	31	48	67	126	272
A9276	SENSOR	127	123	186	228	664
A9277	TRANSMITTER	25	33	55	72	185
A9278	RECEIVER	16	24	18	17	75
	Grand Total	256	282	390	567	1,495

2016 Medicaid HCA
Dollars Paid and Count of Service Units Related to CGM (CPT/HCPCS)
NOTE: Medicaid HCA had 12 Unique Patients in 2016

Code	Description	Paid	Service	Total
95251	AMBULATORY CGM	**$233**	**10**	**$2,329**
A9276	SENSOR	**$3,353**	**4**	**$13,410**
A9277	TRANSMITTER	**$2,486**	**4**	**$9,945**

2014 -2016 Medicaid MCO
Paid Dollars by Year for CGM and Related Items (CPT/HCPCS)

Proc Code	Proc Long Desc - HCPCS	2014	2015	2016	Total
95250	GLUCOSE MONITORING, 72 Hr	$9,716	$6,185	$10,266	**$26,167**
95251	AMBULATORY CGM	$3,740	$4,199	$9,386	**$17,325**
A9276	SENSOR	$719,681	$1,927,402	$3,255,554	**$5,902,637**
A9277	TRANSMITTER	$207,403	$347,211	$725,258	**$1,279,872**
A9278	RECEIVER	$67,185	$108,193	$250,292	**$425,670**
	Grand Total	$1,007,725	$2,393,190	$4,250,756	**$7,651,671**

2013 -2016 Medicaid MCO
Count of CGM Related Units and Average Paid Dollars/Code (CPT/HCPCS)

Proc Code - HCPCS	Proc Long Desc - HCPCS	2014	2014 Avg Pd $	2015	2015 Avg Pd $	2016	2016 Avg Pd $	Total
95250	GLUCOSE MONITORING, 72 Hr	108	$90	73	$85	109	$94	**290**
95251	AMBULATORY CGM	125	$30	168	$25	361	$26	**654**
A9276	SENSOR	1,009	$713	2,742	$703	4,718	$690	**8,469**
A9277	TRANSMITTER	226	$918	386	$900	807	$899	**1,418**
A9278	RECEIVER	38	$829	165	$656	357	$701	**560**
	Grand Total	1,506		3,533		6,352		**11,391**

2. Background

2.1. Epidemiology and Burden of Disease

Self-monitoring of blood glucose (SMBG) and real-time continuous glucose monitoring (CGM) are two techniques that persons with diabetes use at home to help them maintain glucose levels within a safe range. Children and teenagers 18 years old and under with diabetes have the most to gain from maintaining good glucose control yet present some of the greatest challenges in achieving and maintaining good control. As they will probably have many years at risk, children and adolescents with diabetes are at high risk for microvascular complications related to poor glucose control. Intensive treatment with tight control of glucose levels has become the standard of care for diabetes. Such intensive treatment requires monitoring as part of that regimen: by knowing the blood sugar levels the patient or caregiver can adjust diet, exercise, and insulin appropriately. SMBG has become a standard practice recommendation for patients with diabetes. This technical review will assesses the value of real-time CGM for all children, adolescents and adults with type 1 or type 2 diabetes as well as pregnant women with diabetes (either preexisting or gestational) and use insulin, based on the highest quality evidence available. The focus is on evaluation of real-time continuous glucose monitoring to assess glucose levels at home (versus data used exclusively by providers in a clinical setting) for daily decision making regarding self-care. The majority of these patients will have type 1 diabetes. The previous report, which included those ≤18 year old and the a 2012 AHRQ report in adults reported on real-time glucose monitors, thus that is the focus here. This report does not include evaluation of insulin delivery systems (e.g. insulin pumps, multiple daily injections).

Classification of Diabetes Mellitus

Diabetes mellitus, or diabetes, is a serious chronic disease of various etiologies characterized by elevation of blood glucose. No definitive cure is known at this time. Diabetes is categorized into three major types based on etiology

Type 1 diabetes (T1DM) (formerly called juvenile diabetes or insulin-dependent diabetes mellitus (IDDM)), is an autoimmune disorder that destroys the pancreatic beta islet cells where insulin is made. The damage progresses quickly and completely, leading to death within a few weeks without insulin. Type 1 diabetes is the predominant form of diabetes in children but can occur in adulthood.

Type 2 diabetes (T2DM) (formerly called adult onset diabetes mellitus (AODM) or non-insulin dependent diabetes (NIDDM)) is caused by insulin resistance, disordered and inadequate insulin release, and excessive glucose production (gluconeogenesis) in the liver. T2DM is a progressive disease that ultimately requires insulin therapy, although diet, exercise and medications may be effective for the first few years. T2DM occurs more often in adults, but the prevalence in teens and children is increasing. The risk of T2DM is associated with a family history of T2DM, non-white race, obesity, lifestyle and metabolic syndrome.

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy.[101] The glucose elevation occurs in the last half of pregnancy and usually resolves after delivery. GDM is associated with family history of T2DM diabetes and is associated with increased risk of developing T2DM.

Diabetes during pregnancy is defined as women with type 1 or type 2 diabetes who become pregnant[6] and is often described as "pregestational" diabetes. Diabetes during pregnancy often involves frequent changes to insulin requirements, emphasizing the importance of tight glucose monitoring.

Type "other" is a miscellaneous collection of etiologies that damage the beta cell, including infection, cystic fibrosis, trauma, toxins (e.g. alcohol), tumors, and rare genetic disorders. These are uncommon and generally treated like T1DM.

Incidence and Prevalence of Diabetes

In 2015, an estimated 29.9 million Americans (9.3% of the population) had diabetes. By 2050, the projected prevalence of diabetes in the United States population ranges from 21% to 33%.[24] Among children, the prevalence of type 1 diabetes was estimated to be 0.197% in 2015, effecting roughly 180,620 individuals, with a project increase of 13% to 203,385 by 2050.[73] For type 2 diabetes in this population the estimated prevalence was 0.024% in 2015 (roughly 19,704 affected children). The number of children in the United States with type 2 diabetes is expected to increase by approximately 49% by the year 2050.[73] In adults, corresponding prevalence rates are 0.34% for type 1 diabetes (approximately 1.1 million effected individuals) and 6.36% for type 2 diabetes (effecting roughly 12.4 million people). T2DM generally accounts for 95% of all diabetes cases in adults aged 20-64 years[26] and 97.5% of adults aged ≥65 years.[38] Between 0.2% and 0.5% of all pregnancies in the United States are complicated by T1DM each year[53] and although the true prevalence of GDM is unknown, GDM is estimated to affect 1% to 14% of pregnancies in the United States annually.[30,35,72] Some data suggested that the prevalence of GDM in 2010 was between 4.6% and 9.2%.[40]

Morbidity, Mortality and Cost of Diabetes

Diabetic ketoacidosis (DKA) is the leading cause of hospitalization, morbidity and death in children and adolescents with T1DM; its associated mortality rate internationally is 0.15% to 0.3%[94] with idiopathic cerebral edema accounting for two-thirds or more of this mortality. Among all type 1 diabetes-related deaths for patients aged less than 30 years, 54%–76% can be attributed to DKA.[133] DKA is characterized by very high glucose levels, severe dehydration, and acidosis and can quickly lead to coma and death. Risk of DKA is higher in females during menses, children who lack medical resources and miss insulin injections, and those who suffer child neglect.

Chronic complications are similar in T1DM and T2DM and are strongly related to the duration of diabetes and glycemic control.[111] Macrovascular complications consisting of heart disease and stroke are approximately 4 times higher in persons with diabetes than those without. Microvascular complications include retinopathy, nephropathy and neuropathy. Diabetic retinopathy is the leading cause of new cases of blindness among adults ages 20 to 74 years, causing 12,000 to 24,000 new cases of blindness each year. Diabetes is also a major cause of cataracts and glaucoma. In 2007, diabetes was the second leading cause of end-stage renal disease (ESRD), accounting for 44% of new cases of ESRD in the USA.[27] In 2007, 48,172 persons with diabetes started dialysis. A total of 178,689 people with end-stage kidney disease due to diabetes were living on chronic dialysis or with a kidney transplant in the United States and Puerto Rico in 1997.[111] Over 60 percent of persons with diabetes develop mild to severe neuropathy, including distal symmetric polyneuropathy (impaired sensation in feet and hands), mononeuropathy (e.g. carpal tunnel syndrome), erectile dysfunction, and autonomic neuropathy (e.g.

gastric paresis). Neuropathy is a major contributing cause of lower-extremity amputations. More than 60 percent of nontraumatic lower-limb amputations occur in people with diabetes.

Pregnancy related complications are common in women with poorly controlled diabetes. Women with both gestational and preexisting diabetes are at twice the risk of developing gestational hypertension and pre-eclampsia and spontaneous preterm delivery is seen in approximately 20% of diabetic women.[74] Women with type 1 diabetes have the highest risk for preterm delivery and the risk of caesarean delivery is significantly greater with diabetes of any type[76]; reported rates are 52% in type 1, 48% in type 2 and 37% in gestational diabetes.

Other diabetes related complications include increased risk of infections, cancer and other autoimmune disorders including celiac sprue, thyroid disease, rheumatoid arthritis, and vitiligo.

Mortality – Diabetes was the 7th leading cause of death in the United States in 2015, with 79,535 death certificates listing it as the underlying cause of death, and a total of 252,806 death certificates listing diabetes as an underlying or contributing cause of death.[5] Worldwide diabetes was the direct cause of 1.6 million deaths in 2015 and in 2012 high blood glucose was the cause of another 2.2 million deaths.[160]

Costs of diabetes for all persons with diabetes in 2013 exceeded $245 billion. The medical expenditures for persons with diabetes are approximately 2.3 times higher than the expenditures for persons who do not have diabetes. Indirect costs include factors such as increased absenteeism, reduced productivity, and lost productive capacity due to early mortality. About two-thirds of the excess cost of diabetes is due to direct medical expenditures and one-third is attributed to loss of productivity.[4]

Insulin Therapy

For T2DM, oral, non-insulin mediations are generally used initially in combination with lifestyle management education to attain glycemic control. *Insulin therapy* is the only effective therapy for persons with T1DM and is used for T2DM who cannot produce sufficient insulin[6] and pregnant women of any type with elevated glucose.[101] Not all those with T2DM will require insulin. The insulin dose depends on body weight, age, food intake, and activity. Insulin requirements increase with stress, infection, and certain medications (e.g. steroids). Insulin therapy is more effective if it mimics the insulin release pattern in persons without diabetes. About half of the insulin is released continuously, and the other half is released after meals in a quick, large burst. Persons with T1DM also need extra insulin during the night called the dawn effect, but the timing of this increased need varies by pubertal status.[141] Children going through growth spurts have sporadic releases of growth hormone that has some insulin-like effects, further complicating the dosing decisions. Intensive insulin therapy, a term used to describe tight management of blood glucose levels, has been shown to reduce the risk of long-term diabetic complications by lowering average blood sugar levels, but also increases the risk of hypoglycemia, which can result in serious morbidity and even death, and causes fear of hypoglycemia which is a major barrier to optimal glucose control. Insulin may be delivered via multiple daily injections or via continuous subcutaneous insulin infusion using an insulin pump. Greater fluctuation in blood glucose levels may be seen in patients requiring insulin and more attention to monitoring blood glucose levels may be needed.

*Multiple daily injections (MD*I) attempts to mimic the normal insulin release pattern using a long acting insulin for basal insulin coverage once or twice a day and rapid onset insulin injected at each meal. This system attempts to carefully match carbohydrate intake, exercise, and insulin dose and timing. The glucose value obtained from pre-meal testing is used to calculate the correction dose of insulin to return

the glucose to desired goal. The patient then estimates how much insulin will be needed for the upcoming meal and adds that to the correction dose. The final dose is then adjusted for planned activity. Patients benefit from knowing how to do carbohydrate counting, which typically requires an approximation of planned carbohydrate intake, to calculate the needed insulin. The older insulins Regular and NPH didn't mimic the normal insulin release profile very well and were absorbed unreliably. Analog insulins now provide more reliable options for insulin therapy with shorter or longer action to better mimic a natural insulin curve. Routine dietary intake and exercise make it easier to match insulin, but routine is difficult for children.

Continuous subcutaneous insulin infusion (CSII) is a technology that releases insulin from a small pump through a small catheter inserted under the skin that permits greater flexibility in dosing. Pumps may be coupled with CGM, frequently referred to as sensor augmented pump therapy. The electronic controls on the meters allow for changes in the baseline or mealtime dosages. A Cochrane Review of CSII versus MDI published in 2010 found that CSII improved glycemic control (A1C change of -0.3% (95% CI −0.1 to −0.4) reduced severe hypoglycemia, and improved quality of life measures. T[103]he ability to change the insulin dose on a moment to moment basis means that patients generally need to take frequent glucose measurements. CGM is an alternative to performing multiple finger sticks to obtain frequent glucose levels.

Hypoglycemia

Hypoglycemia, or low blood glucose, has often been defined as glucose below 70 mg/dl.[6] Recently, the 2017 version of the American Diabetes Association Standards of Medical Care redefined hypoglycemia into three different levels. The first level, called the glucose alert level, is defined as a blood glucose value equal to or below 70 mg/dl and is considered sufficiently low for the use of fast-acting carbohydrates and a dose adjustment of glucose-lowering therapy. The second level of hypoglycemia is defined as clinically significant hypoglycemia and has a glycemic criteria of a blood glucose level of less than 54 mg/dl. When patients reach this level, their hypoglycemia is considered serious and clinically important. The third and final level is denoted as severe hypoglycemia. Although it does not have specific glycemic criteria, severe hypoglycemia is defined as any hypoglycemia accompanied with severe cognitive impairment that requires external help for recovery. The majority of trials included in this report that provided a definition for severe hypoglycemia were consistent with the ADA definition, explicitly stating that severe hypoglycemia was an episode requiring third party assistance.

Hypoglycemia can occur from too much insulin or exercise or too little food intake. Severe hypoglycemia is defined as the need for assistance, but children and toddlers will also require assistance for recognition and treatment. The body's counter-regulatory mechanisms attempt to stabilize the blood glucose and cause the symptoms that signal impending hypoglycemia. Initial symptoms include hunger, confusion and unsteadiness, followed by diaphoresis, tachycardia, and finally seizures and coma. Persons who have had repeated episodes of hypoglycemia and children under the age of 7 do not experience these warning symptoms and are said to have hypoglycemia unawareness. Hypoglycemia during the night may not be detected until the child has a seizure, but milder hypoglycemia is suggested by night sweats or vivid nightmares. Severe hypoglycemia can damage the developing brain permanently. Two meta-analyses found that children with diabetes have mildly lower cognitive scores across most cognitive domains, and these differences are most pronounced and pervasive for those with early onset diabetes (diagnosis before age 4-7 years).[54,105] Hypoglycemic comas and convulsions have been estimated to occur at a rate of 20 events per 100 patient years in children using conventional therapy.[75] Frequent blood glucose monitoring is critical to identify and prevent hypoglycemia. The goal

is to maintain glucose levels within the target range without increasing risk of hypoglycemia. The target glycemic range outlined by the standards was 80-130 mg/dl for preprandial measurements and anything <180 mg/dl for postprandial measurements. Studies may report target glycemic ranges differently.[8]

Children's smaller size, erratic dietary intake, and unpredictable exercise pattern make it difficult to predict insulin doses to achieve glycemic control without incurring hypoglycemia. [142]The normal developmental issues for children and adolescents of increasing autonomy, peer pressure and desire of "not being different" increase the difficulty of adhering to a rigorous diet, exercise and insulin regimen. Very young children also have limited language and cognitive abilities that impair their ability to detect and report the early signs of hypoglycemia.

Older adults with type 1 diabetes are potentially at increased risk of severe hypoglycemia and may have less capacity to detect and counter-regulated against it[36,96] than younger adults and are more likely to have comorbidities and macro- and micro vascular complications due to longer durations of diabetes. In older patients, hypoglycemia may increase risk for cognitive impairment (temporary or permanent) falls with injury, myocardial infarction, arrhythmias and death.[41,51,137]

Assessment of long-term glucose control

The hemoglobin A1C, or A1C, is a blood test to assess long-term blood glucose control in clinical practice and research settings.[9] The hemoglobin in red blood cells forms a stable bond with glucose, called glycated hemoglobin or A1C. The test reflects the glucose control over the past 90−120 days (the lifespan of a red blood cell) and is reported as the percentage of red blood cells that have been glycated. An A1c value between 5.7 percent and 6.4 percent is considered to be a prediabetes range, with anything above 6.4% indicating a diabetes diagnosis and anything below 5.7 percent considered normal. The National Glycation Hemoglobin Standardization Project (NGSP) was established in 1993 to develop a standards that are now in use test for glycated hemoglobin and improve accuracy of participating laboratories.[92] The A1C test does not provide accurate results for persons with rapid or delayed red cell turnover, such as anemia, hemoglobinopathies, or renal failure. Glycation can occur with other blood proteins.[134] A1C provides an assessment of the average glucose over a time interval, but provide no information on the variability of the glucose levels over that same time interval or to shorter term exposure to hypoglycemia or hyperglycemia.

A1C has become an accepted surrogate outcome measure for risk of developing diabetes complications based on findings from the Diabetes Control and Complications Trial (DCCT).[42,106] Some research suggests that increased variability of glucose levels is associated with increased cardiovascular and other adverse events, however additional research on the impact of glucose variability on health outcomes is needed.[129] The American Diabetes Association[7] suggests that A1C should performed at least two times a year in individuals who are meeting goals and who have stable glycemic control; those who are not meeting glycemic goals or whose therapy has changed should have their A1C tested every 3 months. The A1C goal for non-pregnant adults is <7.0%. For all pediatric age groups <7.5% is recommended. In pregnancy, the target range is 6-6.5%, with less than 6.0% being optimal if it can be achieved without significant hypoglycemia. In older adults with few coexisting chronic illnesses plus intact cognitive and functional status and longer life expectancy, <7.5% is considered a reasonable goal with higher goals for persons with complex health status (multiple coexisting chronic illnesses or substantial impairment to activities of daily living or mild to moderate cognitive impairment) and intermediate life expectancy (<8.0%) and those with very complex health issues (e.g. long-term care, end-stage chronic illness or moderate to severe cognitive impairment or substantial impairment to activities of daily living) with limited remaining life expectancy (<8.5%).[7]

2.2. Technologies/Interventions

Intervention: CGM

Continuous glucose monitoring (CGM) is a technology that measures glucose every few minutes (thus isn't really continuous). SMBG meters measure glucose levels in capillary blood, whereas CMG devices measure glucose in interstitial fluid. The methodology was developed to provide frequent glucose data for persons who had difficulty achieving control or were using CSII. Use of CGM together with CSII is sometimes referred to as sensor augmented pump therapy (SAP).

The Minimed Continuous Glucose Meter System (CGMS) Gold (Medtronic Minimed, Northridge, CA), approved in 1999, was the first CGM approval by the FDA.[85] The meter incorporated glucose oxidase coating on a wire that was placed subcutaneously. Readings were obtained every 5 minutes for 3 days. The meter was directly wired to the sensor, making it difficult to bathe or engage in sports. The accuracy, especially for hypoglycemia, was substandard.[43] Because of the poor accuracy, the FDA specified that CGM should not be used for treatment decisions.[44] Thus, the meter readings were blinded and only available retrospectively. This meter is described in the literature as "retrospective analysis" or "professional analysis data." Most of the early studies of CGM used this meter. In 2005, the FDA approved a new model the Minimed Guardian, which had alarms to alert patients when glucose levels were in ranges for hypo- and hyperglycemia, called for real time data display. This report focuses on real-time CGM. A table of currently approved devices is found below and additional information on devices is available in Appendices J and K.

CGM devices initially received FDA approval to be adjunctive, acting to complement rather than replace SMBG for treatment decisions and therapy modifications and required that sensors be calibrated based on SMBG based on concerns that inaccuracies would lead to inappropriate treatment decisions. The standards for accuracy of CGM are the same for SMBG technology. Accuracy of CGM data is assessed in several ways. The mean absolute difference (MAD) and median absolute difference (MedAD) are computed as the mean/median of the absolute values of the differences between sensor readings and reference blood glucose values. The mean absolute relative difference (MARD) and the median absolute relative difference (MedARD) are the absolute differences expressed as a percentage of the reference blood glucose values. Technological advances and software improvements to real time CGM devices have led to greater accuracy; mean absolute relative deviation (MARD) has decrease from 19.7% in early devices to around 9.0% in more recent devices.[47] Sensor electrode changes to reduce interference from other substances, improvements in algorithms to reduce interference from random electrical noise and reduction in the systematic differences between blood glucose and CGM interstitial glucose measurements, making newer devices more precise and reliable. In addition to improvements in accuracy, advances in more recent devices have addressed some of the technical and human factor limitations present in earlier devices including smaller and more durable sensors, enhanced usability, more audible alarms that can be individualized and easier to read displays. Improvements in CGM devices and technologies have led to increased use clinically and in research. Of the included trials that used a newer device, the average percentage of time of CGM use was 88% to 89% and averaged seven days per week of use. In trials that used older devices the average percentage of time of CGM use was 44% to 90% of time and averaged five days per week of use. Adherence is an important factor for optimal use of CGM.

Technological advances in CGM devices have led to more recent approval of devices for therapeutic (versus adjunctive) use. Within the past year, three devices (T:slim X2 Insulin Pump with Dexcom G5 Mobile CGM system, the Dexcom G5 Mobile CGM System alone, and the Freestyle Libre Flash CGM System) have been FDA approved for non-adjunctive use, allowing them to replace SMBG in making treatment decisions. The MiniMed 670G System has an automatic mode during which the device administers basal insulin at rates based on the glucose values from the CGM device. However, the MiniMed 670G System has not been explicitly approved for making therapy adjustments. All other FDA approved devices required that persons still conduct SMBG several times a day to determine insulin dose decisions and modifications. Apart from the FreeStyle Libre Flash CGM system, which is factory calibrated by the manufacturer, SMBG tests are needed to calibrate CGM devices. While the Libre Flash CGM is included as a CGM device there are important differences between it and other approved devices in the technology and how it is used which are described below. Thus, for purposes of this report, devices will be distinguished as traditional CGM and flash CGM.

Patient education, guidance and support for the appropriate use of CGM devices and the data they generate are needed prior to and during use. Some persons may be overwhelmed by the volume of data available from CGM. Continuous wearing of the sensor may be burdensome and adherence, particularly in children and adolescents, may be problematic. Frequency of alarms in traditional CGM devices may contribute to historical problems with adherence. There is limited evidence on the long-term safety of daily CGM use; frequently cited adverse events include sensor insertion site reactions, skin rashes related to adhesives, sensors falling off, pulling off or sweating off; transmitter or receiver loss, transmission issues at night, sensor malfunction and silencing of alarms (including smart phones in silent or vibrate mode).[120] Considerations for use in pediatric patients include limited body surface area for sensor insertion, difficulty in keeping sensors adhered and how such data from such devices may be used in a school setting.[51]

Traditional CGM

A traditional CGM device consists of a sensor connected to a transmitter that relays information via radiofrequency to a monitoring and display device. All currently FDA approved traditional real-time CGM devices use subcutaneous electrodes coated with glucose oxidase to measure interstitial glucose levels. The glucose oxidase enzyme is embedded onto the sensor, allowing glucose and water to form gluconic acid and hydrogen peroxide. Under a basal electric current, the hydrogen peroxide dissociates, and a modified charge is produced directly proportional to the concentration of the glucose. The electrical current from the enzymatic reaction is measured by the sensor is converted into glucose readings through an internal device algorithm. In all the currently FDA approved traditional CGM systems, the sensors measure glucose levels every 5 minutes. Glucose sensors are inserted subcutaneously and worn externally and must be changed periodically (generally 3 to 7 days). Insertion requires a skin puncture each time a new sensor is placed. (Implantable CGM devices have not yet been FDA approved.) The device sends data continuously to a receiver (including smartphones or smart watches) and data can be downloaded to a computer or smart device to see glucose trends. Alerts and alarms can be provided to the user based on specific thresholds (e.g. for hypoglycemia or hyperglycemia) that can be customized. Data displays vary across device manufactures.

SMBG meters measure glucose levels in capillary blood, whereas CMG devices measure glucose in interstitial fluid. Thus, the CGM value may lag behind the plasma glucose level.[66] This occurs because diffusion of glucose from the capillaries into the interstitial space where it is measured by CGM take anywhere from 5 minutes to 20 minutes, depending on the individual and blood glucose levels.[33] Additionally, the measurement of the glucose by the CGM sensor takes time, usually a couple minutes, before it is displayed. Although the time lag of the CGM sensor itself is not well reported, values may range between 3 and 12 minutes.[33,143] The overall lag time can make the meter appear inaccurate, especially when blood glucose levels are changing quickly.

Flash CGM

In contrast to the traditional CGM devices, the Freestyle Navigator and Freestyle Libre Flash devices use oxidase coupled with osmium-based mediator molecules anchored on a polymeric backbone film termed "wired enzyme" technology. As with traditional devices, glucose sensors are inserted subcutaneously, worn externally and must be changed periodically. Unlike traditional CGM, a transmitter is not worn and no passive glucose information is available to the user. The sensor must be scanned with an external device i.e. by bringing a handheld reader in close proximity (within 1.5" or 4cm) of the sensor. The act of scanning a sensor initiates reader calculations of real-time glucose measurements (glucose values) accompanied by trend information (glucose arrows) and historic eight-hour glucose results (glucose graph) that are presented on a reader display. Glucose values, trend information, and system messages related to high or low glucose values are completely dependent on user-initiated action (a scan). If a patient does not scan the flash glucose monitor, there is no indication or alert of glucose values that are too high or too low. The flash system is factory calibrated. The flash glucose device has less hardware (no transmitter is needed), it does not require calibration from blood glucose measurements, and is FDA approved for longer wear compared to traditional CGM devices.

Comparator: SMBG

Self-monitoring blood glucose (SMBG), sometimes called intermittent monitoring, is a technique for testing blood glucose using a portable glucose meter designed for home use.[134] Glucose meters incorporate paper strips impregnated with glucose oxidase, glucose dehydrogenase, or hexokinase. When a drop of blood is added, these chemicals convert blood glucose into gluconic acid and hydrogen peroxide that can be quantified by colorimetric methods, reflectance photometry, absorbance photometry, or electrochemistry. Whole blood has about 15% less glucose than plasma, so meters translate the result into a plasma equivalent to make the results comparable to results obtained in a clinical lab. The first SMBG meter was approved for home use in 1975 and became the preferred method for home monitoring within a decade[134] and has been a standard for home monitoring.

A more common source of inaccuracy comes from operator-related errors, including calibration failures, poor hand washing, dirty meters, high environmental temperature, improper handling or storage of glucose strips, insufficient sample volume and ingestion of certain drugs (e.g. ascorbic acid, acetaminophen). The meters can download the data into a computer for further analysis or to export to a provider over the internet.

A major barrier to testing is the discomfort associated with puncture of the fingertip. Improvements have been made in recent years however. Improved lancet blade design and devices to control the depth of the prick have made the sample collection process less painful. Recent meters have been approved to test alternate sites on the forearm or thigh, where there are fewer pain receptors. The results from these alternate testing sites is similar to testing from the fingertip before meals (when blood glucose is fairly stable), but the results can differ significantly when the blood glucose is rapidly changing. Fingertip testing is preferred in circumstances of rapidly changing blood glucose levels including after a meal, injection of a rapid acting insulin or exercise.

Other barriers to testing include inconvenience, lack of a private place to test, and lack of safe sharp disposal systems, lack of education on the importance of testing, and costs of the strips. Psychological barriers include the denial and frustration over extreme values. SMBG provides an instantaneous reading of current blood glucose level, but cannot indicate whether the glucose level is on its way up or down.

Summary

Improved methods to monitor blood glucose, especially for hypoglycemia, could make it safer to achieve lower glucose levels. Glucose monitoring should be less intrusive, be easy to use and incorporate into insulin dose changes, and minimize discomfort. Meters intended for use with children need to be smaller and indestructible. The current goal for CGM technology is to integrate with CSII into a "closed loop system" that would eliminate the need for complex management of insulin, diet and exercise.

2.2.3. Indications and Contraindications of CGM

Regarding indications for CGM use, the following is true for all FDA approved CGM devices included in Table 1 below:

- Indicated for detecting trends and tracking patterns in person with diabetes
- Aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments, which may minimize these excursions
- Interpretation of results should be based on the trends and patterns seen with several sequential readings over time
- Single patient use
- Requires a prescription

AND, with the exception of the T:slim X2 Insulin Pump with Dexcom G5 Mobile CGM system, the Dexcom G5 Mobile CGM System, and the FreeStyle Libre Flash CGM System,

- Considered adjunctive; intended to complement, not replace, information obtained from standard home glucose monitoring devices.
    - Not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required.
    - All therapy adjustments should be based on measurements obtained using a home glucose meter and not on the sensor glucose readings provided by the system.
- *The Dexcom G5 Mobile CGM System and the Freestyle Libre Flash CGM System are the only real-time CGM devices approved for therapeutic decision making, as a replacement of traditional fingerstick self-monitoring of blood glucose (SMBG). CGM has been approved for adjustment of insulin therapy in Europe, but not in the United States with the exception of this device.*

- *The T:slim X2 Insulin Pump with Dexcom G5 Mobile CGM system is the only real-time CGM device paired with a pump approved for therapeutic decision making, as a replacement of traditional fingerstick self-monitoring of blood glucose (SMBG).*
- *The Freestyle Libre Flash CGM system is the only CGM system that is factory calibrated and does not required SMBG values for device calibration*

The following are common contraindications to the use of CGM devices (as listed on the SSEDs of FDA approved devices):

- MRI/CT/Diathermy: magnetic fields and heat could damage components of the system which may lead to inaccurate glucose reading or may prevent alerts; device should be removed before undergoing these tests/treatments
- Acetaminophen: may inaccurately raise glucose readings generate by the Dexcom G5; inaccuracy is dependent on amount of acetaminophen active in the body and is different for each person
- Persons unwilling or unable to perform a minimum of 4 blood glucose tests per day (with the exception of the Freestyle Libre Flash CGM system) and to maintain contact with their healthcare professional
- Persons with impaired vision or hearing which does not allow full recognition of the devices' display information and alarms or alerts

Table 1. FDA approved devices

Device name Applicant	PMA#, Approval Date	DM Population	Description/Indication
Stand-alone CGM devices included in 2011 HTA			
Freestyle Navigator CGM System Abbott Diabetes Care, Inc., CA, USA	P050020 March 12, 2008	• Adults (age ≥18 years)	• Stand-alone CGM • Provides real-time readings, graphs, trends and glucose alarms directly to the user for the purpose of improving DM management • Provides a built-in blood glucose meter to confirm the continuous glucose result. • Intended for both in-home use and use in clinical settings
Guardian REAL-Time System Medtronic MiniMed, CA, USA	P980022/S015/ S011 March 8, 2007 (Pediatric version, approved for use in persons age 7-17) June 14, 2006 (original approval, for use in persons age 18 and older)	• Children and adults (ages ≥7 years)	• Stand-alone CGM • Provides real-time readings, graphs, trends and glucose alarms directly to the user for the purpose of improving DM management • Continuous or periodic monitoring of interstitial glucose levels
DexCom STS Continuous Glucose Monitoring System	P050012 March 24, 2006	• Adults (age ≥18 years)	• Stand-alone CGM • Provides real-time readings, graphs, trends and glucose alarms directly to the user for the purpose of improving DM management

Device name Applicant	PMA#, Approval Date	DM Population	Description/Indication
Stand-alone CGM devices included in 2011 HTA			
DexCom, Inc. CA, USA			
CGM + Insulin Pump systems included in 2011 HTA			
Paradigm REAL-Time System Medtronic MiniMed, CA, USA	P980022/S015/ S013 March 8, 2007 (Pediatric version, approved for use in persons age 7-17) April 7, 2006 (original approval, for use in persons age 18 and older)	• Children and adults (ages ≥7 years)	• CGM + Insulin Pump • Continuous or periodic monitoring of interstitial glucose levels (in real-time) for the purpose of improving DM management and/or continuous delivery of insulin (at set and variable rates) via infusion pump
New stand-alone CGM devices			
Freestyle Libre Flash Glucose Monitoring System Abbott Diabetes Care, Inc., CA, USA	P160030 September 27, 2017	• Adults (age ≥18 years)	• Stand-alone CGM • Provides real-time readings and trends of glucose levels directly to the user for the purpose of replacing blood glucose testing for diabetes treatment decisions • **Approved and designed to replace fingerstick blood glucose testing for diabetes treatment decisions** • **The only device that is factory calibrated and does not require calibration from blood glucose measurements**
Dexcom G5 Mobile CGM System Dexcom, Inc. CA, USA	P120005/S041 December 20, 2016 (replace fingerstick blood glucose testing) P120005/S033 August 19, 2015 (mobile application) P120005/S002 February 3, 2014 (expanded age range to ≥2 years) P120005 October 5, 2012 (original PMA; persons age ≥18 years)	• Children and adults (age ≥2 years)	• Stand-alone CGM • Provides real-time readings, graphs, trends and glucose alarms directly to the user for the purpose of improving DM management • Mobile application allows data and alerts to be sent directly to users smart device (Apple/iOS only, though Android compatibility is in the works); Dexcom Share service allows data to be shared in real-time with up to five selected individuals • **Approved for and designed to replace fingerstick blood glucose testing for diabetes treatment decisions**

Device name Applicant	PMA#, Approval Date	DM Population	Description/Indication
Stand-alone CGM devices included in 2011 HTA			
Dexcom G4 PLATINUM CGM System Dexcom, Inc. CA, USA	P120005/S031 May 22, 2015 (approval expanded to include children age 2-17) P120005 October 5, 2012 (original PMA, use in persons ≥18 years)	• Children and adults (age ≥2 years)	• Stand-alone CGM • Provides real-time readings, graphs, trends and glucose alarms directly to the user for the purpose of improving DM management • Works with the Dexcom Share app, which sends real-time glucose values to the cloud, allowing up to five caregivers using Dexcom's Follow app to view real-time glucose readings on Apple or select Android devices • Compatible with the Animas Vibe and Tandem t:slim G4 pumps
New CGM + Insulin Pump systems			
T:slim X2 Insulin Pump with Dexcom G5 Mobile CGM Tandem Diabetes Care, Inc., CA, USA	P140015/S020 August 25, 2017	• Children and adults (age ≥6 years)	• CGM + Insulin Pump • Continuous delivery of basal and bolus insulin at set and variable rates • Updated technology from the t:slim G4 Insulin pump—t:slim X2 pump has been modified to include the functionality of the Dexcom G5 receiver and Dexcom G5 has Bluetooth capabilities that the Dexcom G4 does not • **Only approved CGM and pump system approved to replace fingerstick blood testing for diabetes treatment decisions**
MiniMed 670G System with SmartGuard Medtronic MiniMed, CA, USA	P160017 September 28, 2016	• Adolescents and adults (age ≥14 years)	• CGM + Insulin pump **(closed loop)** • Continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) • SmartGuard technology can be programmed to automatically adjust delivery of basal insulin based on CGM sensor glucose values and can suspend delivery of insulin when the sensor glucose value falls below (or is predicted to fall below) a predefined threshold. • Not intended to be used directly for making therapy adjustments
OneTouch Vibe Plus System* Animas Corporation, PA, USA	P130007/S016 December 16, 2016	• Children and adults (age ≥2 years)	• CGM + Insulin Pump • Consists of Animas Vibe Insulin Pump paired with Dexcom G5 Sensor and Transmitter • Provides continuous subcutaneous insulin infusion and continuous measurements of glucose for up to seven days

Device name Applicant	PMA#, Approval Date	DM Population	Description/Indication
Stand-alone CGM devices included in 2011 HTA			
			• Provides glucose trends, alerts, and a low glucose alarm
MiniMed 630G System with SmartGuard Medtronic MiniMed, CA, USA	P150001 August 10, 2016	• Adolescents and adults (age ≥16 years)	• CGM + Insulin Pump • Continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) and/or for the continuous, real-time monitoring of interstitial glucose levels for the purpose of improving DM management • SmartGuard technology automatically stops insulin delivery for up to 2 hours when glucose values reach a user-selected low threshold and there is no response to the alarm. • Works with CareLink Professional and Personal Therapy Management Software for Diabetes (CareLink Pro, CareLink Personal)
Animas Vibe System* Animas Corporation, PA, USA	P130007/S004 December 24, 2015 (expanded to include age ≥2 years) P130007 November 25, 2014 (original PMA, age ≥18 years)	• Children and adults (age ≥2 years)	• CGM + Insulin Pump • Can be used solely for continuous insulin delivery and to receive and display continuous, real-time glucose measurements (from the Dexcom G4 Platinum CGM System) for the purpose of improving DM management
Paradigm REAL-Time Revel System Medtronic MiniMed, CA, USA	P150019 December 7, 2015	• Adults (age ≥18 years)	• CGM + Insulin Pump • Continuous or periodic monitoring of interstitial glucose levels in real-time for the purpose of improving DM management and/or continuous delivery of insulin (at set and variable rates) via infusion pump
t:slim G4 Insulin Pump/"t-slim G4 System" Tandem Diabetes Care, Inc., CA, USA	P140015 September 8, 2015	• Adolescents and adults (age ≥12 years)	• CGM + Insulin Pump • Can be used solely for continuous insulin delivery and as part of the t:slim G4 System and to receive and display continuous, real-time glucose measurements (from the Dexcom G4 Platinum CGM System) for the purpose of improving DM management
MiniMed 530G System	P120010 September 26, 2013	• Adolescents and adults	• CGM + Insulin Pump • Continuous delivery of basal insulin (at user selectable rates) and administration of insulin

Device name Applicant	PMA#, Approval Date	DM Population	Description/Indication
Stand-alone CGM devices included in 2011 HTA			
Medtronic MiniMed, CA, USA		(age ≥16 years)	boluses (in user selectable amounts) and/or for the continuous, real-time monitoring of interstitial glucose levels for the purpose of improving DM management • SmartGuard technology automatically stops insulin delivery for up to 2 hours when glucose values reach a user-selected low threshold and there is no response to the alarm. • Works with CareLink Professional and Personal Therapy Management Software for Diabetes (CareLink Pro, CareLink Personal)
EXCLUDED			
Freestyle Libre Pro Flash Glucose Monitoring System Abbott Diabetes Care, Inc., CA, USA	September 23, 2016 P150021	• Adults (age ≥18 years)	• Professional CGM device only. The System is intended for use by health care professionals to aid in the review, analysis, and evaluation of a patient's glucose readings in support of an effective diabetes management program; Readings from the FreeStyle Libre Pro sensor are only made available to patients through consultation with a health care professional.
iPro2 CGM System Medtronic, Inc. Diabetes, CA, USA	June 17, 2016 P150029 (for use with the Enlite sensor) P980022/S071 (approved in 2011 for use with the Sof-Sensor)	• Unclear	• 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

CGM: continuous glucose monitoring; PMA: Premarket Approval
*As of October 2017, pumps manufactured by Animas are no longer commercially available

2.3. Clinical Guidelines

The National Guideline Clearinghouse (NGC), PubMed, Google and Google Scholar and references of included studies were searched for guidelines related to the use of continuous glucose monitoring. Updated versions of all guidelines included in the previous report were looked for. Key word searches (and combinations of key word searches) performed included: ("continuous glucose monitoring" OR "glucose monitoring"), "type 1 diabetes", "type 2 diabetes", "children", "adolescents", "pediatric", "adult", ("pregnancy" OR "pregnant" OR "pregnant women").

Guidelines were obtained from the following organizations (additional guidelines unaffiliated with an organization were also found):

- American Diabetes Association (ADA)
- Joslin Diabetes Center
- The Endocrine Society
- American Association of Clinical Endocrinologists (AACE)
- American College of Endocrinology
- National Institute for Health and Clinical Excellence (NICE)
- National Collaborating Centre for Women and Children's Health

Consensus statements were found from the following organizations (additional consensus statements unaffiliated with an organization were also found):

- American Association of Clinical Endocrinologists (AACE)
- American College of Endocrinology
- International Society for Pediatric and Adolescent Diabetes (ISPAD)
- Italian Society for Pediatric Endocrinology and Diabetes (ISPED)

Thirteen guidelines and four consensus statement documents were Details of each included recommendation for the use of continuous glucose monitoring in diabetes are summarized below.

Table 2. Summary of clinical guidelines

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
American Diabetes Association (ADA)* [7] Standards of Medical Care in Diabetes (2017)	1 meta-analysis 4 RCTs 1 registry study 3 studies, type NR	CGM **may be a useful tool** in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. Individual readiness **should be assessed** prior to prescribing CGM. Robust diabetes education, training, and support **are required** for optimal CGM implementation and ongoing use. *Adult population*	C† E† E†

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		CGM, when used properly and in conjunction with intensive insulin regimens, **is a useful tool** for lowering A1C levels in selected adults (aged 25 years or older) with T1DM. People who have been using CGM successfully **should have continued access** after they turn 65 years old. *Pediatric population* CGM **may be helpful** for lowering A1C levels in children, teens, and younger adults.	A† E† B†
Joslin Diabetes Center and Joslin Clinic (Shahar et al.) [140] Clinical guideline for adults with diabetes (2015, revised 2017)	1 RCT 2 studies, type NR	For patients using RT-CGM to treat hypoglycemia, blood glucose levels should be checked 15 minutes post treatment using a finger stick and not the sensor reading. CGM **can be considered** if the patient has a history of severe recurrent hypoglycemia or hypoglycemia unawareness.	1B‡ NR
Peters et al. [118] Diabetes Technology—Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline (2016)	<u>T1DM in adults</u> 7 studies, type NR <u>T2DM in adults</u> 1 RCT 1 study, type NR	RT-CGM **is recommended** for adults patients with T1DM who have A1C levels above target and who are willing and able to use devices on a nearly daily basis. RT-CGM **is recommended** for adult patients with well-controlled T1DM who are willing and able to use devices on a nearly daily basis. **It is suggested** that short-term, intermittent RT-CGM is used in adult patients with T2DM (not on prandial insulin) who have A1C levels at 7% or greater and are willing and able to use the device. **It is suggested** that adults with T1DM and T2DM who use CSII and CGM receive education, training, and ongoing support to help achieve and maintain individualized glycemic goals.	1, A§ 1, A§ 2, C§ Ungraded Good Practice Statement

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
Handelsman et al. [60] American Association of Clinical Endocrinologists and American College of Endocrinology—Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)	2 RCTs	CGM **should be considered** for patients with T1DM and T2DM on intensive insulin therapy to improve A1C levels and reduce hypoglycemia. CGM **may benefit** patients not taking insulin.	Grade B, BEL 2** Grade D, BEL 4**
Blumer et al. [21] Diabetes and pregnancy: an Endocrine Society clinical practice guideline (2013)	NR	CGM **is suggested** for use during pregnancy in women with overt or gestational diabetes when self-monitored blood glucose levels (or HbA1C values in women with overt diabetes) are not sufficient to assess glycemic control	2++††
Klonoff et al.‡‡ [86] Continuous Glucose Monitoring: An Endocrine Society Clinical Practice Guideline (2011)	<u>T1DM in children and adolescents</u> 3 RCTs 11 studies, type NR <u>T1DM in adults</u> 2 RCT 5 studies, type NR	RT-CGM **is recommended** for children and adolescents with T1DM who have achieved HbA1c levels below 7.0%. RT-CGM **is recommended** for children and adolescents with T1DM with T1DM who have HbA1c levels of 7.0% or higher who are able to use devices on a nearly daily basis. **No recommendations are made for or against** the use of RT-CGM in children with T1DM who are less than 8 years old.	1, A§ 1, B§ NA§
NICE [112] 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) (2016)	NR	The MiniMed Paradigm Veo system **is recommended** as an option for managing blood glucose levels in people with T1DM only if: • They have episodes of disability hypoglycemia despite optimal management with CSII *and* • The company arranges to collect, analyze, and publish data on the use of the	NR

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		MiniMed Paradigm Veo system The MiniMed Paradigm Veo system **should be used under** the supervision of a trained multidisciplinary team who are experienced in CSII and CGM for managing T1DM only if the person or their carer: • Agrees to use the sensors for at least 70% of the time • Understands how to use it and is physically able to use the system *and* • Agrees to use the system while having a structured education program on diet and lifestyle, and counselling People who start using the MiniMed Paradigm Veo system **should only continue use it** if there is a sustained decrease in the number of hypoglycemic episodes. There is **insufficient evidence** for the Vibe and G4 PLATINUM CGM to support routine adoption in the National Health Service for managing blood glucose levels in people with T1DM.	
NICE (National Clinical Guideline Centre) [108] Type 1 diabetes in adults: diagnosis and management (2015)	NR	**Do not offer** RT-CGM routinely in adults with T1DM. RT-CGM **can be considered** for adults with T1DM willing to commit to using at least 70% of the time and to calibrate the device as needed, and who have any of the following characteristics despite optimized use of insulin therapy and conventional BGM: • > 1 episode of severe hypoglycemia per year with no	NR

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		obviously preventable precipitating cause • Complete loss of awareness of hypoglycemia • Frequent (>2) episodes per week of asymptomatic hypoglycemia that causes problems with daily activities • Extreme fear of hypoglycemia • Hyperglycemia (HbA1c levels of 9% or higher) that persists despite testing at least 10 times per day. RT-CGM **should only be continued** if HbA1c can be sustained at or below 7% and/or there has been a fall in HbA1c levels of 2.5% or more Adults with T1DM using RT-CGM should use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or CSII therapy. RT-CGM should be provided by a center with expertise in its use, as a part of strategies to optimize a person's HbA1c levels and reduce frequency of hypoglycemic episodes.	
National Collaborating Centre For Women and Children's Health [109] Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015)	NR	Offer ongoing RT-CGM with alarms to children and young people with T1DM who have at least 1 of the following: • Frequent severe hyperglycemia • Impaired awareness of hypoglycemia associated with adverse consequences (e.g. seizures or anxiety) • Inability to recognize or communicate about symptoms of hypoglycemia (e.g. cognitive or neurological disabilities)	NR

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
		Offer ongoing RT-CGM for: • Neonates, infants, and pre-school children • Children and young people who have undertaken high levels of physical activity • Children and young people who have comorbidities or who are receiving treatments that can make blood glucose control difficult CGM **can be considered** to help improve blood glucose control in children and young people who continue to have hyperglycemia despite insulin adjustment and additional support.	
National Collaborating Centre For Women and Children's Health [110] Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (2015)	NR	**Do not offer** CGM routinely to pregnant women with diabetes. CGM **can be considered** for pregnant women on insulin therapy if one of the following applies: • Problematic severe hypoglycemia (with or without impaired awareness of hypoglycemia) • Unstable blood glucose levels (to minimize variability) • To gain information about variability in blood glucose levels **Ensure that support is available** for pregnant women who are using continuous glucose monitoring from a member of the joint diabetes and antenatal care team with expertise in its use.	NR
Wright et al. [161] A Practical Approach to the Management of Continuous Glucose	1 SR 2 RCTs 13 studies, type NR	Continuous CGM **can be considered** for any patient irrespective of age, sex, socioeconomic status, ethnic, or educational background who meet NICE criteria§§.	B***

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
Monitoring (CGM) / Real-Time Flash Glucose Scanning (FGS) in Type 1 Diabetes Mellitus in Children and Young People Under 18 Years (2017)		Continuous CGM **can be considered** in children on CSII or MDI therapy. Continuous CGM with alarms **should be considered** in any child of any age who has had a hypoglycemic seizure. Continuous CGM with alarms **should be considered** in all young children. Continuous CGM with alarms **should be considered** in all children of any age with neurodevelopmental or cognitive problems that impair their ability either to recognize or respond to hypoglycemia. CGM with alarms **should be considered** in frequent hypoglycemia and in nocturnal hypoglycemia. CGM with alarms **should be considered** in situations with individuals who have unawareness of hypoglycemia. CGM with alarms **should be considered** in individuals where anxiety or fear of hypoglycemia is high. CGM **can be considered** for improving diabetes control in children and young people by reducing HbA1c and/or reducing the time spent in hypoglycemia, with any HbA1c < 10%. CGM **is not recommended** for use to reduce HbA1c or hypoglycemia in children with HbA1c > 10%.	A*** B*** A*** D*** B*** B*** D*** B*** D***
Choudhary et al. [31] Evidence-Informed Clinical Practice Recommendations for Treatment of Type 1 Diabetes Complicated	2 SRs 4 RCTs 1 observational study 4 studies, type NR	CSII or CGM **should be added** to the treatment regimen of patient's with T1DM and problematic hypoglycemia if glycemic and hypoglycemia targets are not met though an education or hypoglycemia-specific education program.	NR

Guideline	Evidence Base	Recommendation	Rating/Strength of Recommendation
by Problematic Hypoglycemia (2015)			
Working Group of the Clinical Practice Guideline on Diabetes Mellitus Type 1 [159] Clinical practice guidelines for diabetes type 1 (2012)	NR	CGM **can be used** as an instrument to improve or maintain metabolic control in patients motivated and trained in intensive care. However, CGM **is not recommended for universal use** for people with T1DM.	A***

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1c (glycated hemoglobin); MDI, Multiple Daily Injection; NICE, National Institute for Health and Care Excellence; NR, not reported; RCT, randomized controlled trial; RT-CGM, real-time continuous glucose monitoring; SR, systematic review; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

* Chamberlain 2016 details the ADA Standards of Medical Care from 2016. The paper supports the use of CGM for the reduction of severe hypoglycemia risk but gives no additional recommendations for CGM

†ADA evidence-grading systems for "Standards of Medical Care in Diabetes"

A: Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including

- Evidence from a well-conducted multicenter trial
- Evidence from a meta-analysis that incorporated quality ratings in analysis

Compelling nonexperimental evidence, i.e. "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford.

Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including

- Evidence from well-conducted trials at one or more institutions
- Evidence from meta-analysis that incorporated quality ratings in the analysis

B: Supportive evidence from well-conducted cohort studies

- Evidence from a well-conducted prospective cohort study or registry
- Evidence from a well-conducted meta-analysis of cohort studies

Supportive evidence from a well-conducted case-control study

C: Supportive evidence from poorly controlled or uncontrolled studies

- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
- Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)
- Evidence from case series or case reports

Conflicting evidence with the weight of evidence supporting the recommendation

E: Expert consensus or clinical experience

‡ Strength of recommendation grading:

1A: strong recommendation and high quality of evidence
1B: Strong recommendation and moderate quality of evidence
1C: Strong recommendation and low quality of evidence
2A: Weak recommendation and high quality of evidence
2B: Weak recommendation and moderate quality of evidence

2C: Weak recommendation and low quality of evidence

§GRADE Strength of Recommendation:

1: Strong for an intervention
2: Weak for an intervention
3: Weak against an intervention
4: Strong against an intervention

GRADE Quality of Evidence rating:

A: High quality of evidence
B: Moderate quality of evidence
C: Low quality of evidence
D: Very low quality of evidence

** Strength of recommendation grading:

A: Strong
B: Intermediate
C: Weak
D: Not evidence based

Best evidence level (BEL) grading:

1: Meta-analysis of randomized controlled trials (MRCT) OR randomized controlled trials (RCT)
2: Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT) OR nonrandomized controlled trial OR prospective cohort study (NRCT) OR prospective cohort study (PCS) OR retrospective case-control study (RCCS)
3: Cross-sectional study (CSS) OR surveillance study (SS) OR consecutive case series (CCS) OR single case reports (SCR)
4: No evidence; based on theory, opinion, consensus, review, or preclinical study (NE)

††Quality of evidence and strength of recommendation grading:

Quality of evidence:

+ denotes very low quality evidence
++ denotes low quality evidence
+++ denotes moderate quality evidence
++++ denotes high quality evidence

Strength of recommendation:

1-indicates a strong recommendation
2-indicates a weak recommendation

‡‡Recommendations for adult populations were not included because updated guidelines from the Endocrine Society for adult populations are in Peters et al.

§§NICE criteria was stated as patients with the following indications: hypoglycemic seizures, frequent severe hypoglycemia, impaired awareness of hypoglycemia, anxiety regarding hypoglycemia, inability to recognize hypoglycemia due to cognitive or neurological disabilities, young children who may not be able to recognize and respond, patients undertaking high levels of physical activity, to reduce HbA1c, to improve glycemic control, or to reduce glycemic variation

***Strength of recommendation grading:

A: At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*
A body of evidence consisting principally or studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1++ or 1+
C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2++
D: Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2+

Table 3. Summary of consensus statements

Consensus statement	Evidence Base	Recommendation	Rating/Strength of Recommendation
Danne et al. International Consensus on Use of Continuous Glucose Monitoring (2017)	**Type 1** 12 studies, type NR **Type 2** 3 studies, type NR **Gestational diabetes** 1 study, type NR	CGM **should be considered** in conjuction with HbA1c for glycemic status assessment nd therapy adjustment in all patients with type 1 and patients with type 2 diabetes treated with intesnsive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia Al patients **should receive training** in how to interpret and respond to their glucose data. Patient education and training for CGM should utilized standardized programs with follow-up to improve adherence and facilitate appropriate use of data and diabetes therapies. CGM data **should be used** to assess hypoglycemia and glucose variability	NR
Bailey et al. [12] American Association of Clinical Endocrinologists and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement (2016) **Fonseca et al.*** [50] Continuous Glucose Monitoring: A Consensus Conference of the American Association of Clinical Endocrinologists and American College of Endocrinology (2016)	<u>T1DM</u> 1 study, type NR 1 nonrandomized study 2 RCT <u>T2DM</u> 2 RCTs <u>Gestational Diabetes</u> 1 study, type NR 3 RCTs	CGM **should be available** to all insulin-using patients regardless of diabetes type, although **data on CGM is limited** in patients with T2DM receiving insulin/sulfonylureas or glinides. **No recommendation** can be made for CGM in patients with T2DM that have a low risk of hypoglycemia *Adult population* CGM is **recommended** in adults with T1DM, particularly in patients with history of severe hypoglycemia, hypoglycemia unawareness, and to assist in the correction of hyperglycemia in patients not at goal. *Pediatric population* CGM is **recommended** in children with pediatric T1DM, particularly in	NR

Consensus statement	Evidence Base	Recommendation	Rating/Strength of Recommendation
		patients with history of severe hypoglycemia, hypoglycemia unawareness, and to assist in the correction of hyperglycemia in patients not at goal. More in-depth training and more frequent follow-up is recommended. *Pregnant population* CGM **can be used** during pregnancy as a teaching tool, to evaluate glucose patterns, and to fine-tune insulin dosing. CGM in pregnancy **can supplement BGM** particularly to monitor nocturnal hypoglycemia or hyperglycemia and postprandial hyperglycemia.	
Rewers et al. [128] ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Assessment and monitoring of glycemic control in children and adolescents with diabetes (2014)	2 RCTs 8 studies, type NR	CGM devices are becoming available that **may particularly benefit** those with hypoglycemic unawareness.	A†
Kesavadev et al. [83] Consensus guidelines for glycemic monitoring in type 1/type 2 & GDM (2014)	<u>T1DM in adults and adolescents</u> 2 studies, type NR <u>T1DM in youth</u> 5 studies, type NR	CGM **may be a supplemental tool** to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. *Adult population* CGM in conjunction with intensive insulin regimens **can be useful** in lowering A1C in selected adults (age ≥25 years) with type 1 diabetes. *Pediatric population* CGM **may be helpful** in children, teens, and younger adults in lowering A1C levels.	D‡ A‡ C‡

Consensus statement	Evidence Base	Recommendation	Rating/Strength of Recommendation
		CGM **is recommended** in children and adolescents with T1DM who have achieved HbA1c levels less than 7.0%. CGM **is recommended** in youth with T1DM who have HbA1c levels 7.0% or higher and are able to use the device on a near-daily basis. *Pregnant population* Pregnant patients with T1DM **should be offered** CGM	D‡ D‡ Rating NR
Scaramuzza et al. [135] Recommendations for self-monitoring in pediatric diabetes: a consensus statement by the ISPED (2013)	2 SRs 3 RCTs 9 studies, type NR	Patients should fulfill the following criteria to be a candidate for CGM: • Children with no awareness of hypoglycemia or frequent episodes of severe hypoglycemia • Children and adolescents with impaired metabolic control (HbA1c > 8.5%) on intensive insulin therapy CGM **could be helpful** in the following circumstances: • To improve metabolic control regardless of HbA1c value • To reduce SMBG measurements, especially if > 10 times per day • To help patients undergoing competitive sports • To start insulin pump therapy	NR

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c (glycated hemoglobin); ISPAD, International Society for Pediatric and Adolescent Diabetes; ISPED, Italian Society of Pediatric Endocrinology and Diabetology; NR, not reported; RCT, randomized controlled trial; SMBG, self-monitoring blood glucose; SR, systematic review; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

*Fonseca et al. was associated with the same consensus conference as Bailey et al; emphasis for information on recommendations was placed on Bailey et al. while Fonseca et al. was used for background information and context.
† System for rating strength of recommendation was not reported
‡ Strength of recommendation grading:

A: Type of evidence supporting recommendation is based on randomized controlled trials, meta-analyses, or systematic reviews
B: Type of evidence supporting recommendation is based on non-randomized controlled trials or uncontrolled randomized clinical trials
C: Type of evidence supporting recommendation is based on observational trials or evidence based reviews or case studies
D: Type of evidence supporting recommendation is based on opinion of expert panel

2.4. Previous Systematic Review/Technology Assessments

Systematic reviews and health technology assessments (HTAs) were found by searching PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Guideline Clearinghouse from May 2010 to 10/23/2017. Reviews published since the previous report were selected for summary with a focus on those of highest quality. Reference lists of relevant studies and the bibliographies of systematic reviews were hand searched. See Appendix B for search terms and full search strategy.

Table 4. Selected Previous Health Technology Assessments and Systematic Reviews

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
AHRQ (2012) Effective Health Care Program CER [55] Agency for Healthcare Research Quality *Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness* **Yeh et al. (2012)** [162] *Comparative Effectiveness and Safety of Methods of Insulin Delivery and Glucose Monitoring for Diabetes Mellitus*	Database inception to July 2011	Diabetes (Type 1 or Type 2)	**Treatments:** rt-CGM vs. SMBG **Key Qs:** Compared to SMBG, does rt-CGM have a differential effect on process measures, intermediate outcomes, and clinical outcomes? Do effects differ by a) Type 1 or Type 2, b) age, c) pregnancy status, or d) MDI vs. CSII?	rt-CGM vs. SMBG: n = 9 RCTs (Adults and children with Type 1, requiring insulin) SAP vs. MDI/SMBG: n = 4 RCTs (Adults and children with Type 1, requiring insulin)	**rt-CGM vs. SMBG:** **Microvascular and macrovascular disease** No studies provided in any of the populations of interest. **HbA_{1c}** Adults, Type 1 (n=9 RCTs): rt-CGM resulted in larger reduction in patients with Type 1 (strength of evidence, high); MD = -0.30% (95% CI: -0.37 to -0.22%, p<0.001). Children, Type 1 (n=4 RCTs): rt-CGM resulted in larger reduction in patients with Type 1 (strength of evidence, high); MD = -0.26% (95% CI: -0.46 to -0.06%, p=0.248). **Severe hypoglycemia** Adults and children, Type 1 (n=8 RCTs): No difference (strength of evidence, low); Pooled RR = 0.95 (95% CI: 0.53 to 1.69). **Nonsevere hypoglycemia** Adults and children, Type 1 (n=7 RCTs): No difference (strength of evidence, moderate); MD = -2.11 minutes/day (95% CI: -5.66 to 1.44 minutes/day, p=0.515). **Hyperglycemia** Adults and children, Type 1 (n=6 RCTs): rt-CGM resulted in less time in hyperglycemic state (strength of evidence, moderate); MD =-68.56 minutes/day (95% CI: -101.17 to -35.96 minutes/day, p=.326). **General QOL** Adults and children, Type 1 (n=3 RCTs): No difference (strength of evidence, low).

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					Diabetes specific QOL Adults and children, Type 1 (n=2 RCTs): No difference (strength of evidence, low). **Diabetes treatment-related QOL** Adults and children, Type 1 (n=1 RCT): No difference (strength of evidence, insufficient). No studies reported outcomes in pregnant women with pre-existing diabetes, adults or children with Type 1 that do not require insulin, nor adults or children with Type 2, regardless of insulin requirement.
Riemsma et al. (2016) Health Technology Assessment [130] National Institute for Health Research *Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation*	Database inception to September 2014	Diabetes (Type 1)	**Treatments:** SAP vs. CSII+SMBG SAP vs. MDI+SMBG **Key Qs:** What is the clinical effectiveness of SAP compared with: -CSII+SMBG -MDI+SMBG -CSII+CGM -MDI+CGM? What is the cost effectiveness of SAP compared with: -CSII+SMBG -MDI+SMBG -CSII+CGM -MDI+CGM?	SAP vs. CSII+SMBG (n = 4 RCTs) SAP vs. MDI+SMBG (n=4 RCTs)	**SAP vs. CSII+SMBG** **HbA_{1c}** Adults, Type 1 (n=1 RCT): No significant difference (no SoE reported); WMD = -0.05% (95% CI: -0.31% to .21%). Children, Type 1 (n=3 RCTs): No difference (no SoE reported); MD = 0.4894% (SE: 0.2899%). **Hypoglycemia** Adults, Type 1 (n=2 RCTs): SAP resulted in decreased rate of hypoglycemic events (no SoE reported). Children, Type 1 (n=1 RCT): SAP resulted in a lower rate of hypoglycemic events (no SoE reported). **QOL** Adults, Type 1 (n=4 RCTs): SAP resulted in better quality of life (no SoE reported); WMD = 5.90 (95% CI: 2.22 to 9.58). **SAP vs. MDI+SMBG**

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					HbA_{1c} Adults, Type 1 (n=3 RCTs): SAP resulted in larger reduction (no SoE reported); WMD = -0.05% (95% CI: -1.46% to -0.741%). Children, Type 1 (n=1 RCT): SAP resulted in larger reduction (no SoE reported); MD = -0.05% (95% CI: -0.8% to -0.2%). **Hypoglycemia** Adults, Type 1 (n=4 RCTs): No difference (no SoE reported). Children, Type 1 (n=1 RCT): No difference (no SoE reported). **Hyperglycemia** Adults, Type 1 (n=2 RCTs): No significant difference (no SoE reported). **QOL** Adults, Type 1 (n=4 RCTs): SAP resulted in better quality of life (no SoE reported); WMD = 8.60 (95% CI: 6.28 to 10.92). Children, Type 1 (n=1 RCT): No difference (no SoE reported). No studies reported on micro- or macro-vascular outcomes. No studies reported in pregnant women nor adults or children with Type 2.
Matsuda (2014) [95]	2002 to 2012	Diabetes (Type 1)	**Treatment** CGM vs. SMBG	n = 2 RCTs	**HbA_{1c}**

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
The effectiveness of continuous glucose monitoring for type 1 diabetic adolescents using continuous subcutaneous insulin infusion pumps: a systematic review			**Key Qs** Are metabolic outcomes improved in outpatient adolescents with T1DM on a CSII pump when CGM is used as compared to SMBG alone?		Children, Type 1 (n=2 RCTs): No significant difference at 26 weeks (no SoE reported); MD = -0.11 (95% CI: -0.61 to 0.39, p=0.674). No studies reported on micro- or macro-vascular outcomes, hypoglycemia, hyperglycemia, or QOL. No studies reported outcomes in pregnant women, adults, children with Type 1 that do not require insulin, nor children with Type 2.
Poolsup (2013) [124] *Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes*	Database inception to May 2013	Diabetes (Children with Type 1 and Adults with Type 2)	**Treatment** CGM vs. SMBG **Key Qs** What are the effects of CGM on glycemic control in children with Type 1 and adults with Type 2 diabetic?	Children, Type 1: n = 10 RCTs Adults, Type 2: n = 4 RCTs	**HbA_{1c}** Children, Type 1 (n=10 RCTs): CGM resulted in greater reduction (strength of evidence, low); MD = -0.13% (95% CI: -0.38% to 0.11%, p=0.27). Adults, Type 2 (n=4 RCTs): CGM resulted in greater reduction (strength of evidence, low); MD = -0.31% (95% CI: -0.60% to -0.02%, p=.04). No studies reported on micro- or macro-vascular outcomes, hypoglycemia, hyperglycemia, or QOL. No studies reported outcomes in pregnant women, adults with Type 1, nor children with Type 2.
Voormolen (2013) [155] *The Efficacy and Effectiveness of Continuous Glucose Monitoring During Pregnancy: A Systematic Review*	Database inception to February 2013	Diabetes (Type 1, Type 2, or GDM)	**Treatment** CGM vs. SMBG **Key Qs** What is the efficacy and the effectiveness of CGM in pregnancy?	CGM vs. SMBG: n = 2 RCTs (Pregnancy, Type 1 or Type 2)	**Fetal outcomes** Pregnancy, Type 1 or Type 2 (n=2 RCTs): No difference in any outcomes other than macrosomia. One of the two studies found significantly less macrosomia in the CGM group while the other found no difference (no SoE reported). **HbA_{1c}** Pregnancy, Type 1 or Type 2 (n=2 RCTs): No difference (no SoE reported).

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					No studies reported on micro- or macro-vascular outcomes, hypoglycemia, hyperglycemia, or QOL. No studies reported outcomes in pregnant women with GDM, non-pregnant adults nor children.
Meade (2012) [100] *The Use of Continuous Glucose Monitoring in Patients with Type 2 Diabetes*	2000 to May 2010	Diabetes (Type 2)	**Treatments** CGM **Key Qs** What is the clinical evidence for using CGM in patients with type 2 DM?	n = 5 RCTs n = 7 observational studies	**HbA_{1c}** All ages, Type 2 (n=5 RCTs, n=7 observational studies): Conflicting results (no SoE reported). **Hypoglycemia** All ages, Type 2 (n=5 RCTs, n=7 observational studies): Conflicting results (no SoE reported). **Hyperglycemia** All ages, Type 2 (n=5 RCTs, n=7 observational studies): Conflicting results (no SoE reported). No studies reported on micro- or macro-vascular outcomes or QOL. No studies reported outcomes in pregnant women nor adults or children with Type 1.
Langendam et al. (2012) [90] *Continuous glucose monitoring systems for type 1 diabetes mellitus*	Database inception to June 2011	Diabetes (Type 1)	**Treatments** CGM vs. SMBG CGM system vs. another type of CGM system **Key Qs** What are the effects of CGM systems compared with each other and compared to conventional SMBG in patients with T1DM?	n= 22 RCTs (includes both retrospective and real-time systems) Adults, T1 n=11 Children, T1 n=10: Adolescents, T1 n=2	**ALL AGES** **HbA_{1c}** All patients, Type 1 (n=2 RCT) the mean change in HbA1c was lower for CGM than control (strength of evidence, moderate); 0.7 lower (0.8 to 0.5 lower) **Severe Hypoglycemia** All patients, Type 1 (n=1 RCT) CGM resulted in a higher risk of severe hypoglycemia at 6 months than control (strength of evidence, very low); RR 3.26 (95% CI0.38 to 27.82) **Diabetic Ketoacidosis**

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					All patients, Type 1 (n=1 RCT) CGM resulted in a higher risk at 6 months (strength of evidence, very low); RR 2.45 (95% CI0.1 to 58.45) **QOL - Physical Health Domain** All patients, Type 1 (n=1 RCT) CGM resulted in a slightly higher mean quality of life (strength of evidence, very low); 91 vs 92.3; 1.3 higher (95% CI4.2 lower to 6.8 higher) **QOL - Mental Health Domain** All patients, Type 1 (n=1 RCT) CGM resulted in a slightly higher mean quality of life (strength of evidence, very low); 91 vs 92.3; 1.3 higher (95% CI4.2 lower to 6.8 higher) **ADULTS (≥24)** **HbA_{1c}** Adults (≥24), Type 1 (n=5 RCTS): CGM resulted in a statistically significant decrease in HbA1c at 3 months (varying between -0.1% and 1.1%,3 RCTs, no SoE reported) and at 6 months for 2 RCTs; after 12 months the change in HbA1c was larger for the CGM vs. SMB (-1.0% vs. -0.4%, MD -0.6%, 95% CI-0.5% to -0.4%, 1 RCT, no SoE reported); CGM saw a larger proportion of patients improved their HbA1c with at least 0.5% (46% versus 11%, RR 4.25%, 95% CI 1.76 to 10.22, 1 RCT); no significant differences were found at 18 months (1 RCT, no SoE reported) **CGM-derived Hypoglycemia and Hyperglycemia** CGM-derived hypoglycaemia, measured as percentage of time, was significantly shorter

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					for CGM compared to SMBG(22% vs. 38%,MD 17%, 95% -25%to -8%, 1 RCT, no SoE reported) **Severe Hypoglycemia and Diabetic Ketoacidosis** No significant differences were found at 3, 6 and 12 months (4 RCTs, no SoE reported) **QoL** No significant differences were found at 6 months (2 RCTs, no SoE reported) **CHILDREN** **HbA_{1c}** Children (≤14), Type 1 (n=3 RCTs): CGM resulted in a significant difference in HbA1c levels at 3 months (no SoE reported); (-0.5% vs. -0.2%; MD in change -0.2% (95% CI-0.3% to 0.0%) No difference at 6 and 12 months (no SoE reported). Children (≤14), Type 1 (n=1 RCTs): Statistically significant difference in proportion of patients who improved HbA1c levels at least 0.5% favoring the CGM group at 3 months (46% vs. 28%; RR 1.68, 95% CI1.02 to 2.78, 1 RCT) and at 6 months (54% vs. 31%, RR 1.73, 95% CI1.10 to 2.72, 1 RCT). **Severe Hypoglycemia** Children (≤14), Type 1 (n=3 RCTs): No significant differences were found at 6 months or 12 months (no SoE reported). **Diabetic Ketoacidosis** No significant differences were found at 6 months or 12 months

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					QoL Children (≤14), Type 1 (n=2 RCTs) No significant differences were found at 6 months or 12 months **Cost-Effectiveness** Not measured in any of the studies with Children or adolescents. **ADOLESCENTS(15-23)** **HbA_{1c}** Adolescents (15-23), Type 1 (n=2 RCTS): No significant differences were found (no SoE reported). **Hypoglycemia** Adolescents (15-23), Type 1 (n=2 RCTS): No significant differences were found (no SoE reported). **Severe Hypoglycemia and Diabetic Ketoacidosis** No significant differences were found (no SoE reported). **QoL** Not measured in any of the studies with adolescents. **Cost-Effectiveness** Not measured in any of the studies with Children or adolescents.
Moy et al. (2017) [104] *Techniques of monitoring blood glucose during pregnancy for*	Database Inception to November 2016	Diabetes (Type 1, Type 2)	**Treatments** SMBG vs standard care, SMBG vs hospitalization, SMBG before meals vs. after meals, Glucose Monitoring,	N = 10 RCTs	**CGM vs Intermittent CGM:** **Maternal HbA_{1c}** Women, pre-existing DM (n=1 RCTs): rt-CGM resulted in a greater end of treatment reduction in HbA1c(strength of evidence, moderate); -0.60 (95% CI0.91 lower to 0.29 higher)

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
women with pre-existing diabetes			Automated monitoring vs conventional system, CGM vs intermittent monitoring, Constant CGM vs. intermittent CGM **Key Qs** What is the comparative effectiveness and impact of different techniques of blood glucose monitoring on maternal and infant outcomes among pregnant women with pre-existing diabetes		**Pre-eclampsia** Women, pre-existing DM (n=2 RCTs): rt-CGM resulted in an increased risk for pre-eclampsia (strength of evidence, low); RR 1.37 (95% CI0.52 to 3.59) **Caesarean Section** Women, pre-existing DM (n=2 RCTs): No significant differences were found (strength of evidence, very low); RR 1.00 (95% CI0.65 to 1.54) **Large-for-gestational age** Women, pre-existing DM (n=2 RCTs): CGM resulted in a reduced risk of births classified as large-for-gestational age (strength of evidence, very low); RR 0.89 (95% CI0.41 to 1.92) **Perinatal Mortality** Women, pre-existing DM (n=1 RCT): CGM resulted in a reduced risk of perinatal mortality (strength of evidence, low); RR 0.82 (95% CI0.05 to 12.61) **Preterm birth less than 37 weeks** Women, pre-existing DM (n=2 RCTs): CGM resulted in a higher risk of preterm birth less than 37 weeks (strength of evidence, low); RR 1.10 (95% CI0.63 to 1.94) **Gestational hypertension and preterm birth less than 34 weeks** Not measured in any of the included studies. **Constant CGM vs Intermittent CGM:** **Maternal HbA_{1c}**

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					Women, pre-existing DM (n=1 RCTs): rt-CGM resulted in a slightly greater reduction in end of treatment HbA1c(strength of evidence, very low); -0.09 (95% CI0.69 lower to 0.51 higher) **Caesarean Section** Women, pre-existing DM (n=1 RCT): CGM resulted in a reduced risk of Caesarian section (strength of evidence, very low); RR 0.77 (95% CI0.33 to 1.79) **Maternal Blood Glucose Levels** Women, pre-existing DM (n=1 RCT): rt-CGM resulted in a slightly greater reduction in end of treatment HbA1c(strength of evidence, very low); -0.14 (95% CI2.00 lower to 1.72 higher) **Preterm birth less than 37 weeks** Women, pre-existing DM (n=1 RCTs): CGM resulted in a slightly higher risk of preterm birth less than 37 weeks (strength of evidence, low); RR 1.08 (95% CI0.08 to 15.46) **Gestational hypertension, Pre-eclampsia, Large-for-gestational age, Perinatal Mortality and preterm birth less than 34 weeks** Not measured in any of the included studies.
Pickup et al., (2011) [122] *Glycaemic control in type 1 diabetes during real time*	Database inception to June 2010	Diabetes (Type 1)	**Treatments** rtCGM vs. SMBG	N = 6 RCTs	**HbA_{1c}** Adults, Type 1: rt-CGM resulted in greater reduction in HbA1c values (no SoE reported); MD: -0.30 (95% CI: -0.43 to -0.17) (-3.0, -4.3 to 1.7 mmol/mol)

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data			**Key Qs** What is the clinical effectiveness of rt-CGM compared with self-monitoring of blood glucose in patients with type 1 diabetes?		**AUC Hypoglycemia** Adults, Type 1: rt-CGM resulted in greater reduction in AUC values (no SoE reported); -0.28 (-0.46 to -0.09) reduction of 23% compared to SMBG
Benkhadra (2017) [18] *Real-time continuous glucose monitoring in type 1 diabetes: a systematic review and individual patient data meta-analysis*	Database inception to January 2015	Diabetes (Type 1)	**Treatments** rt-CGM vs. control **Key Qs** Does rt-CGM help in the management of individuals with Type 1?	n = 11 RCTs	**HbA_{1c}** Adults, Type 1: rt-CGM resulted in greater reduction (no SoE reported); MD: -0.258 (95% CI: -0.464 to -0.052, p=0.014). Children (≤12), Type 1: No difference (no SoE reported); MD: -0.047 (95% CI: -0.217 to 0.124, p=0.592). Children (13-15), Type 1: No difference (no SoE reported); MD: -0.039 (95% CI: -0.320 to 0.242, p=0.787). **Severe hypoglycemia** Adults (>15), Type 1: No difference (no SoE reported); MD: -0.074 (95% CI: -0.517 to 0.368, p=0.742). Children (≤12), Type 1: No difference (no SoE reported); MD: 0.392 (95% CI: -0.070 to 0.854, p=0.097).

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					Children (13-15), Type 1: No difference (no SoE reported); MD: 0.536 (95% CI: -0.243 to 1.316, p=0.177). **Nonsevere hypoglycemia** Adults, Type 1: No difference (no SoE reported); MD: -8.095 minutes (95% CI: -32.615 to 16.425, p=0.518). Children (≤12), Type 1: No significant difference (no SoE reported); MD: -9.366 minutes (95% CI: -19.898 to 1167, p=0.081). Children (13-15), Type 1: No significant difference (no SoE reported); MD: -13.0965 (95% CI: -31.782 to 3.852, p=0.124). No studies reported on micro- or macro-vascular outcomes or QOL. No studies reported outcomes in pregnant women nor adults or children with Type 2.
Vigersky (2015) [153] *The Benefits, Limitations, and Cost-Effectiveness of Advanced Technologies in the Management of Patients With Diabetes Mellitus*	Not reported	Diabetes (Type 1 and Type 2)	**Treatments** rt-CGM SAP **Key Qs** 1. What is the evidence that technology can improve A1c and/or reduce the risk of hypoglycemia? 2. What are the limitations in using technology to accomplish this?	rt-CGM: n = 4 economic studies n = 2 meta-analyses SAP: n = 1 economic study n = 1 meta-analysis n = 1 RCT	**rt-CGM** **HbA_{1c}** All patients (n=2 meta-analyses): rt-CGM resulted in larger reduction compared to SMBG (no SoE reported). **Hypoglycemia** All patients (n=2 meta-analyses): reduction in rate of hypoglycemia is proportionate to baseline A1C (no SoE reported). **Cost-Effectiveness** All ages, Type 1 (n=3 studies): CGM is more cost-effective than SMBG (no SoE reported); ICERs between $45,033 and $98,679/QALY gained.

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
			3. What is the cost-effectiveness of technology?		All ages, Type 2 (n=1 study): rt-CGM is cost-effective (no SoE reported); ICER = $8,896/QALY gained. **SAP** **HbA_{1c}** All patients (n=1 RCT, n=1 meta-analysis): SAP resulted in larger reduction compared to SMBG (no SoE reported). **Hypoglycemia** All patients (n=1 meta-analysis): No difference (no SoE reported). **Cost-Effectiveness** All ages, Type 1 (n=1 studies): SAP is cost-effective than SMBG (no SoE reported); ICER = $40,908/QALY gained.
Ontario HTA (2011) [62] Continuous Glucose Monitoring for Patients with Diabetes	Jan 1, 2002 to Sep 15, 2010	Diabetes (Type 1 or Type 2)	**Treatments:** CGM+SMBG vs. SMBG alone **Key Qs:** What is the effectiveness and cost-effectiveness of CGM combined with SMBG compared to SMBG alone in the management of diabetes?	n = 2 RCTs (Adults and children with Type 1, requiring insulin)	**Microvascular and macrovascular disease** No studies provided in any of the populations of interest. **HbA_{1c}** Adults and children, Type 1 (n=2 RCTs): No difference (strength of evidence, moderate); MD = -0.18 (95% CI: -0.38 to -0.03, p=0.09). **Severe hypoglycemia** Adults and children, Type 1 (n=1 RCTs): CGM+SMBG resulted in significantly more severe hypoglycemic events (strength of evidence, moderate); p=0.04. **Hyperglycemia** Adults and children, Type 1 (n=2 RCTs): Significant o difference (strength of evidence, moderate).

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated and Key Questions	Evidence Base Available	Primary Conclusions
					No studies reported on microvascular or macrovascular outcomes or QOL. No studies reported outcomes in pregnant women, nor adults or children with Type 2.

AUC: area under curve; CGM: continuous glucose monitoring; CI: confidence interval; CSII: continuous subcutaneous insulin infusion; DM: diabetes mellitus; HbA1c: hemoglobin A1c; ICER: incremental cost effectiveness ratio; MD: mean difference; MDI: multiple daily injections; QALY: quality-adjusted life year; QOL: quality of life; RCT: randomized control trial; RR: risk ratio; rt-CGM: real-time continuous glucose monitoring; SAP: sensor-augmented pump therapy; SMBG: self-monitoring blood glucose; SoE: strength of evidence; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

2.5. Medicare and Representative Private Insurer Coverage Policies

Coverage decisions are summarized briefly below and policy details are provided in Table 5. In the policies listed below, home blood glucose monitors (SMBG) are covered for the management of diabetes mellitus and a number of insurance carriers now cover continuous glucose monitoring (CGM) as well. Overall, most coverage policies found CGM devices as a replacement for SMBG to be medically necessary for short-term usage from 72 hours up to 14 days. Overview of payer assessments and policies for SMBG and CGM are found in the table below. The listing is not meant to include policies of all private insurers offering coverage in Washington, instead it offers policies representative of the current state of CGM coverage (requirements for this report are to provide information on Medicare NCD and information on two bell-weather payers.)

- **Medicare**

Medicare does not have an NCD on CGM systems; however there is an NCD on home blood glucose monitors. These and related accessories and supplies are considered medically necessary and are covered as long as certain criteria are met by the patient or the patients' care giver. CMS updated their policy on CGM devices in a ruling (CMS Ruling 1682R) published on January 12, 2017. This ruling separated CGM devices into therapeutic and non-therapeutic devices, and allows for therapeutic devices to be considered as durable medical equipment (DME). Therapeutic devices are those used as a replacement for fingerstick BG testing for diabetes treatment decisions (i.e. used as a primary system and not as an adjunct) and must meet five criteria used to classify DMEs. The ruling does not establish CGM broadly as medically necessary but does allow for claim-by-claim payment for devices approved for therapeutic uses.

- **Cigna**

Home blood glucose monitoring as well as CGM are considered medically necessary and are covered in all patients with type 1 diabetes as long as certain criteria are met. Specifically relating to younger persons, long-term CGM is medically necessary in type 1 diabetes who are < age 25 years AND have recurrent severe hypoglycemic events despite appropriate modifications in insulin therapy and compliance with frequent self-monitoring of blood glucose (≥ 4 times /day).

- **Blue Cross/Blue Shield**

CGM is covered in the short term (72 hours) for patients with type 1 diabetes who primarily have poorly controlled diabetes despite best the current use of best practices, pregnant individuals with insulin-treated T1 or T2 diabetes, individuals with T1 DM and requires determination of basal insulin level measurements prior to insulin pump initiation, and individuals with T1 or T2 DM with documentation of certain criteria. In the case of long-term patients, CGM is covered for recurrent, unexplained, symptomatic episodes of severe hypoglycemia and pregnant patients with poorly controlled DM.

• **United Healthcare**

United Healthcare considers external insulin pumps that deliver insulin by continuous subcutaneous infusion as proven and medically necessary for T1DM Patients and for patients with T2DM who currently perform ≥4 insulin injections and ≥4 blood glucose measurements daily. Short-term (3-7 days) CGM covered for diagnostic purposes is proven and medically necessary for patients with diabetes. Long-term CGM usage is considered medically necessary as a supplement to self-monitoring of blood glucose (SMBG) for patients with T1DM who have demonstrated adherence to a physician ordered diabetic treatment plan.

Table 5. Overview of payer policies

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
Centers for Medicare and Medicaid Services **National Coverage Decision (2008)** ***Updated CMS policy ruling 2017***	• NR	Eligibility for coverage of home blood glucose monitors and related accessories and supplies is based on the patient and/or patient's caregiver meeting the following criteria: ▪ Diagnosis of diabetes ▪ Physician's statement on the patient's capability of being trained to use the particular device prescribed in an appropriate manner. ▪ The device is a designated for home rather than clinical use. Blood glucose monitoring systems with special features are covered under Medicare if the above criteria are met and the patient's physician certifies that the patient has a visual impairment severe enough to require use of special monitors. A policy ruling (CMS Ruling 1682R) published on January 12, 2017 separated CGM devices into therapeutic and non-therapeutic devices, and allows for therapeutic devices to be considered as durable medical equipment (DME). Therapeutic devices are those used as a replacement for fingerstick BG testing for diabetes treatment decisions (i.e. used as a primary system and not as an adjunct) and must meet five criteria used to classify DMEs. The criteria for DME classification includes: ▪ Approval by the FDA for use in place of a BGM for making diabetes treatment decisions (for example, changes in diet and insulin dosage) ▪ The device is generally not useful to the individual in the absence of an illness or injury ▪ Is appropriate for use in the home, and ▪ Includes a durable component (that can withstand repeated use and has an expected lifetime of at least 3 years) that is capable of displaying the trending of the continuous glucose measurements The ruling does not establish CGM broadly as medically necessary but does allow for claim-by-claim payment for devices approved for therapeutic uses. To qualify for Medicare coverage of therapeutic CGM, beneficiaries must meet all of the following criteria: • 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	• Rationale not reported Covered if selection criteria are met: • CPT/HCPCS codes: 82947, 82948, 82962, A4233, A4234, A4235, A4236, A4244, A4245, A4246, A 4247, A4250, A4253, A4255, A4256, A4257, A4258, A4259, A9275, A9276, A9277, A9278, E08.00-E23.0 E0607, E0620, E2100, E2101, O16.5-O24.93 • ICD-10 codes: 249.00–249.91,

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
		• 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.	
BlueCross BlueShield Corporate Medical Policy (2017)	▪ FDA approved devices ▪ Various meta-analyses, SRs, RCTs	For short-term interstitial CGMS devices, no more than two continuous glucose monitoring periods may be considered medically necessary within a 12-month period. Short-term interstitial CGMS monitoring is intended only for periodic or occasional testing and to supplement, not replace, self-testing of blood glucose. <u>Short-term CGM is considered by BCBS medically necessary for individuals meeting any one of the following criteria:</u> ▪ Individuals is a pregnant female with insulin-treated T1 or T2 DM ▪ Individual is a pregnant female who develops gestational diabetes (defined as any degree of glucose intolerance with onset or first recognition during pregnancy, which requires insulin therapy) ▪ Individual with T1 DM and requires determination of basal insulin level measurements prior to insulin pump initiation ▪ Individual has T1 or T2 DM, and has documentation of all of the following: ▪ Received diabetes self-management education and instruction from a healthcare professional with diabetes management expertise ▪ Documented average of at least three glucose self-tests per day during the prior month ▪ On an intensive insulin regimen, requiring two or more insulin injections per day, or uses an insulin pump ▪ Has one or more of the following while on an intensive insulin regimen: • Glycated hemoglobin (HbA1c) values less than four or greater than nine • Unexplained large fluctuations in daily glucose values before meals • Unexplained frequent hypoglycemic attacks (greater than one per week or three per month)	Covered if selection criteria are met: ▪ <u>CPT Codes:</u> 95250, 95251, 99091 95250, 95251 ▪ <u>HCPCS codes:</u> A4225, A9276–A9278, K0553, K0554 ▪ <u>ICD-10 codes:</u> E08.00, E08.01, E08.10, E08.11, E08.311, E08.319, E08.3211-E08.3213, E08.3291, E08.21, E08.22, E08.29, 250.00–250.93, 333.91, 648.00–648.04, 648.80–648.84,

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
		• Episodes of ketoacidosis or hospitalizations for significantly elevated glucose levels • Hypoglycemic episodes without experiencing warning and recognition of symptoms or hypoglycemic unawareness which puts the patient or other at risk. Continuous or Long-term Monitoring of glucose (including real-time monitoring) is may be considered medically necessary when one of the following criteria is met despite best practice guidelines: ▪ Recurrent, unexplained, life threatening (blood glucose levels less than 50 mg/dL) hypoglycemia putting the patient or others at risk ▪ Pregnant patient whose diabetes is poorly controlled	
Cigna Medical Coverage Policy (2017)	▪ ADA 2017 recommendations NICE guidelines ▪ various meta-analyses, SRs, RCTs and case series (Schutt, et al., 2006; Sarol, et al., 2005; Welschen, et al., 2005; Soumerai, et al., 2004 Inzucchi and Sherwin, 2007)	<u>Either of the following SMBG devices are covered and considered medically necessary when used for the management of diabetes mellitus:</u> ▪ A standard home blood glucose monitor ▪ An enhanced feature glucose monitor for individuals with a visual or severe manual dexterity impairment <u>Minimally invasive CGM systems are considered medically necessary for up to 14 days under the core medical benefits plan for:</u> ▪ the management of 'difficult to control' insulin-treated DM (e.g. hypo- or hyperglycemic episodes unresponsive to adjustments, asymptomatic nocturnal hypoglycemia) ▪ up to six separate sessions in any given 12-month period <u>Cigna covers minimally invasive CGM systems as medically necessary for the management of T1 or T2 DM when used according to U.S. FDA approved indications and all of the following criteria are met:</u> ▪ completion of a self-management education program for diabetes ▪ treatment programs including at least 3 insulin injections per day with frequent self-adjustments for at least 3 months ▪ documented blood glucose self-testing average of at least four times per day during the two months prior to commencing insulin pump usage ▪ Any of the following while on multiple daily injection regimen: o Glycated hemoglobin level (HbA1c) > 7.0% o History of recurring hypoglycemia o Wide fluctuations in blood glucose before mealtime	Policy is in accordance with FDA and ADA recommendations, and NICE guidelines Policy is in accordance with FDA and ADA recommendations Policy is in accordance with ADA and NICE recommendations Covered if selection criteria are met: ▪ HCPCS Codes: A9277, A9278, E0607, E2100, E2101 ▪ CPT® code: 95250, 95251

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
		○ Dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dL ○ History of severe glycemic excursions	
United Healthcare Medical Policy (2017)	AMA, AACE/ACE, Endocrine Society and ADA guidelines, various systematic reviews, meta-analyses, RCTs, AHRQ CER (Golden et al. 2012),	<u>The following criteria determine coverage for CGM based on short and long term usage:</u> ▪ Short-term (3-7 days) continuous glucose monitoring by a healthcare provider for diagnostic purposes is proven and medically necessary for patients with diabetes. ▪ Long-term continuous glucose monitoring for personal use at home is proven and medically necessary as a supplement to self-monitoring of blood glucose (SMBG) for patients with type 1 diabetes who have demonstrated adherence to a physician ordered diabetic treatment plan. ▪ Long-term continuous glucose monitoring for personal use at home is unproven and not medically necessary for patients with type 2 diabetes or gestational diabetes ▪ Continuous glucose monitoring using an implantable glucose sensor is investigational, unproven and not medically necessary due to lack of U.S. Food and Drug Administration (FDA) approval.	Covered if selection criteria are met: ▪ CPT codes: 0403T, 0447T, 0448T, 95250, 95251 ▪ HCPCS codes: A9274–A9278, E0607, E0784, E1399, S1030, S1031, S1034-S1037

AACE: American Association of Clinical Endocrinologists; ADA: American Diabetes Association; AST: alternate site testing; CGM: continuous glucose monitoring; CPT: Current Procedural Terminology; DME: durable medical equipment; FDA: Federal Drug Administration; HCPCS: Healthcare Common Procedure Coding System; HTA: health technology assessment; ICD-9: International Statistical Classification of Diseases and Related Health Problems; NICE: National Institute for Health and Clinical Excellence; RCT: randomized controlled trial; SMBG: self-monitoring blood glucose; SR: systematic review

3. The Evidence

3.1. Methods of the Systematic Literature Review

3.1.1. Objectives

The primary aim of this report is to update the 2011 HTA on glucose monitoring in children and adolescents by systematically reviewing, critically appraising and analyzing new research evidence on the safety and efficacy of continuous glucose monitoring in persons under 18 years old with insulin requiring diabetes mellitus. The second aim is to systematically review, critically appraise and analyze research evidence on the safety and efficacy continuous glucose monitoring in persons with type 1 or type 2 diabetes (regardless of insulin requirement), including pregnant women with pre-existing or gestational diabetes. SMBG as a stand-alone means of monitoring blood glucose will not be included as an intervention. This report does not include evaluation of insulin delivery systems (automated or other).

3.1.2. Key Questions

In persons with diabetes mellitus (DM):

1. What is the evidence of efficacy and effectiveness of continuous monitoring?
2. What is the evidence of the safety of continuous glucose monitoring?
3. What is the evidence that glucose monitoring has differential efficacy or safety issues in subpopulations?
4. What is the evidence of cost-effectiveness of continuous glucose monitoring?

3.1.3. Inclusion/exclusion criteria

Inclusion and exclusion criteria are summarized in Table 6. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Persons with diabetes mellitus, including those with type 1 and type 2, and pregnant women with pre-existing diabetes or gestational diabetes
- **Interventions:** FDA-approved real-time continuous glucose monitoring devices and FDA-approved combination devices integrating real-time continuous glucose monitoring with insulin pump/infusion (including sensor augmented insulin pumps)
- **Comparators:** Self-monitoring using convention blood glucose meters, attention control, blinded or sham CGM and usual care. Comparisons of one CGM device with another with another will be excluded
- **Outcomes:** Primary clinical outcomes are 1) microvascular complications, 2) macrovascular complications, 3) fetal outcomes, cesarean section rates. Primary intermediate outcomes are 1) achieving target (i.e. age-appropriate) HgA1C level, 2) maintaining target (i.e. age-appropriate)

HgA1C level, 3) acute episodes of hypoglycemia. Safety outcomes are 1) mortality, 2) morbidity from glucose meters or monitors. Economic outcomes are cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcomes.

- **Studies:** Studies must report at least one of the primary clinical or primary intermediate outcomes. Focus will be on studies with the least potential for bias (i.e., randomized controlled trials). Comparative observational studies with long term clinical outcomes or safety will also be considered. Full economic studies will be considered for cost-effectiveness.

Table 6. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	• Persons with diabetes mellitus including those with type 1 or type 2 diabetes • Pregnant women with pre-existing diabetes or gestational diabetes	• Studies in patients with maturity onset diabetes of the young, as the diagnosis is difficult to make without genetic testing
Interventions	• FDA-approved, real-time continuous glucose monitoring devices • FDA approved combination devices integrating real-time continuous glucose monitoring with insulin pump/infusion (including sensor augmented insulin pumps)	• Continuous glucose monitors collecting only data to be used retrospectively • Non-FDA–approved continuous glucose monitors • Non-FDA approved combination devices (monitor + pump) • Devices that are no longer being marketed • Monitors whose results are used only in a clinician's office or laboratory (i.e., Professional CGMs). • Tests for urine glucose, urine ketones, serum beta-hydroxybutyrate, colorimetric strips • Studies comparing accuracy of devices and feasibility • Studies of alternate anatomic sites for monitoring • Stand-alone fingerstick self-monitoring of blood glucose (SMBG)
Comparator	• Self-monitoring using conventional blood glucose meters • Attention control, sham/blinded CGM • Usual care	• Comparisons of one CGM device with another • Urine testing
Outcomes	**Primary Clinical Outcomes** • Microvascular complications (e.g., vision loss, kidney failure, peripheral neuropathy, objectively assessed) • Macrovascular complications (e.g., coronary artery, cerebrovascular or peripheral arterial disease, objectively assessed) • Fetal outcomes*, cesarean section rates **Primary Intermediate Outcomes**	• Other intermediate outcomes • Fructosamine levels

Study Component	Inclusion	Exclusion
	• Achieving target (i.e., age-appropriate) HgA1C level • Maintaining target (i.e., age-appropriate) HgA1C level • Acute episodes of hypoglycemia **Secondary Intermediate Outcomes** • Acute episodes of hyperglycemia • Acute episodes of diabetic ketoacidosis • Quality of life (validated instruments only) **Safety** • Mortality • Morbidity from glucose meters or monitors **Economic** • Long term and short term comparative cost-effectiveness (e.g., ICER, cost savings for prevented morbid event)	
Study Design	• Only high quality (low risk of bias) comparative studies (e.g., randomized controlled trials, crossover trials) will be considered for questions 1-3. • Observational studies (e.g., longitudinal studies correlating intermediate outcomes (e.g., HgA1C) with long term clinical outcomes (e.g. macro or microvascular outcomes, maternal or fetal outcomes)) will be considered for questions 1 and 3; observational studies of safety will be considered; • Formal, full economic studies will be sought for question 4. Studies using modeling may be used to determine cost-effectiveness over the full duration of glucose monitoring, which is a lifetime.	• Studies other than comparative studies with concurrent controls for questions 1-3 • Studies of low quality (high risk of bias) • Studies with fewer than 10 per treatment arm • Case reports • Case series • Studies assessing the reliability and validity of glucometers or continuous monitors • Studies comparing modes of therapy (i.e. multiple daily injections (MDI) vs. external continuous subcutaneous insulin infusion (CSII) via insulin pump) • Studies comparing different types of CGMs with each other. • Studies comparing intermittent and continuous monitoring
Publication	• Studies published in English in peer reviewed journals, technology assessments or publically available FDA reports • Studies published subsequent to the 2011 report (Search date through July 8, 2010) for persons <18 years old and studies published subsequent to the 2012 AHRQ (search date through July 2011) report for adults, those with type 2 diabetes requiring insulin and pregnant women • For question 4, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal	• Abstracts, editorials, letters • Duplicate publications of the same study that do not report different outcomes or follow-up times • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when full results are published in later versions • Incomplete economic evaluations such as costing studies

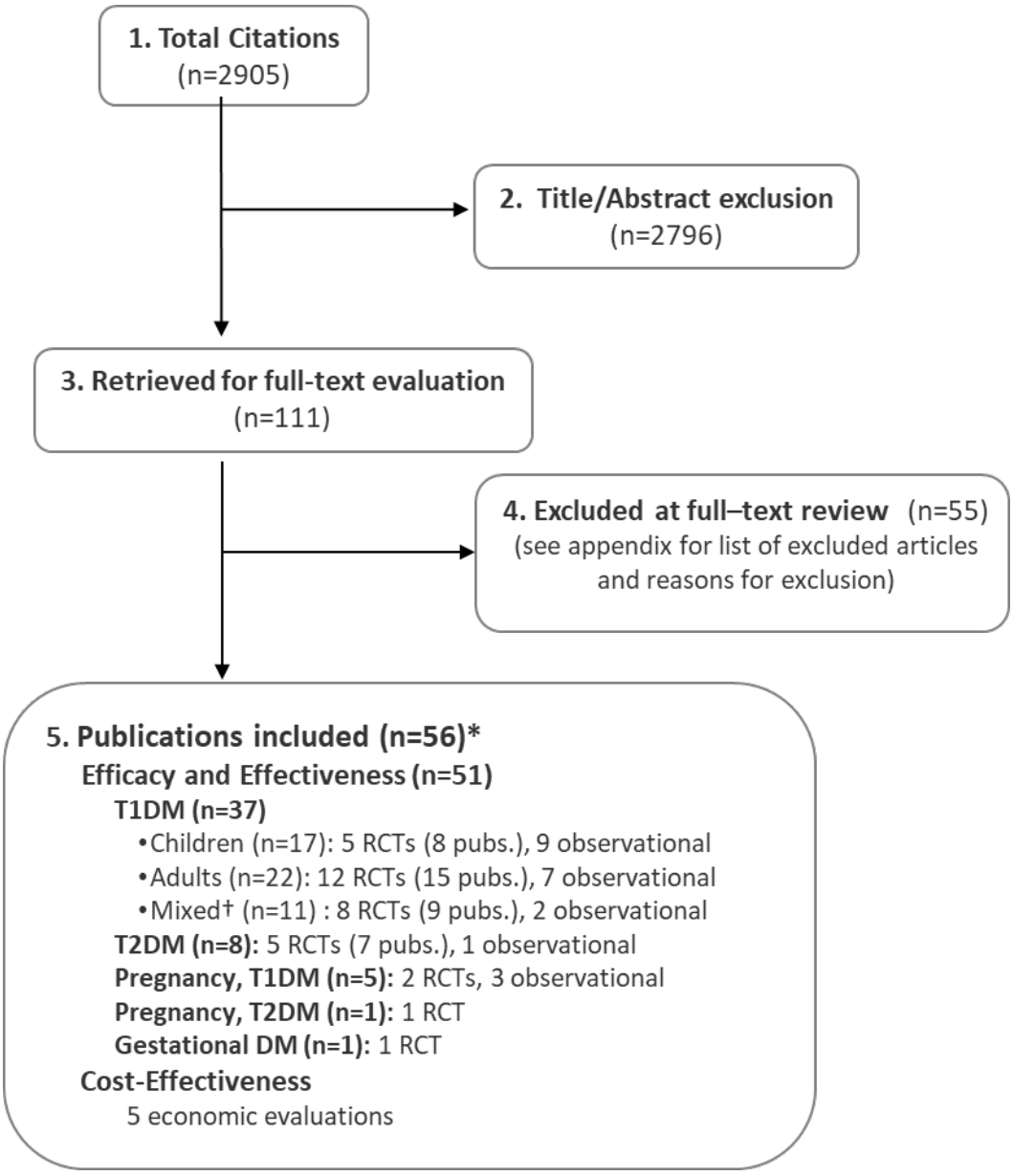
*Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit, stillbirth, and neonatal and perinatal mortality.

3.1.4. Data sources and search strategy

We searched electronic databases from May 2010 to July 26, 2017 to identify publications assessing real-time use of continuous glucose monitoring that had been published since the original report as well as since the 2012 AHRQ report in adults. Our 2011 report served as a basis for updating information on people ≤18 years old requiring insulin and a 2012 AHRQ report served as a base source of RCTS for other populations and is summarized in the report background. Electronic databases searched include PubMed, EMBASE the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Guideline Clearinghouse (see Appendix B for full search strategy). We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of the comprehensive electronic search and bibliography check. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria were included. Articles were selected for full-text review if they included a comparison of an intervention and a control of interest for the treatment of chronic migraine, chronic tension-type headache, or chronic daily headache. We excluded conference abstracts, non-English-language articles, and studies of nonhuman subjects. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of *a priori* inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary adjudicated by a third investigator. A list of excluded articles along with the reason for exclusion is available in Appendix C. The remaining articles form the evidence base for this report, Figure 2.

Figure 2. Flow chart of literature search results



DM: diabetes mellitus; pubs.: publications; RCT: randomized controlled trial; T1DM: type 1 diabetes; T2DM: type 2 diabetes.
*A publication may contribute data to more than one type of diabetes.
†Refers to a mixed population of children and adults.

3.1.5. Data extraction

Reviewers extracted the following data from the clinical studies: study design, study period, setting, country, sample size, inclusion and exclusion criteria, study population characteristics, study interventions, follow-up time, characteristics of the control intervention, study outcomes and adverse events. Information on how continuous glucose monitoring was used to make treatment modifications was also abstracted. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. Detailed study and patient characteristics is available in Appendix F, all results are available in the results section of this document and in Appendices G and H.

3.1.6. Quality assessment: Overall Strength of evidence (SoE), Risk of Bias, and QHES evaluation

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SoE) for each primary outcome from RCTs are based on criteria and methods established in the *Cochrane Handbook for Systematic Reviews of Interventions*,[65] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,[11] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[1,157] Criteria for assessment of cross-over trials were adapted from the Cochrane Handbook and other publications. Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[116] Based on these quality criteria, each study chosen for inclusion for a Key Question was given a RoB (or QHES) rating; details of each rating are available in Appendix E. Standardized, pre-defined abstraction guidelines were used to determine the RoB (or QHES) rating for each study included in this assessment.

The SoE for all primary health outcomes was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[13,56,57] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[1] The strength of evidence was based on the highest quality evidence available for a given outcome. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results that are similar in terms of effect sizes, range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head to head).
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing or selective reporting.

When assessing the SoE for studies performing subgroup analysis, we also considered whether the subgroup analysis was preplanned *(a priori)* and whether a test for homogeneity or interaction was done.

Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the observational studies could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified if there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs. Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

3.1.7. Analysis

Evidence was summarized separately for type 1 and type 2 diabetes as well as diabetes during pregnancy, to include pre-existing type 1 and 2 and gestational diabetes. Within each of the categories, results were further summarized separately by age group (children, adults and mixed children and adults) to the extent that data were available. Some trials contributed data to more than one of the above strata.

Two general types of randomized controlled trials were considered for this review: the more traditional parallel design and cross-over trials. In parallel RCTs, patients are randomly allocated to specific groups and remain in those groups throughout the duration of the trial. In cross-over trials, patients receive different treatments at different time periods. Cross-over trials offer some benefits when used appropriately, e.g. fewer subjects are needed and each patient serves as he/his own matched control enhancing statistical power. This design however is subject to unique sources of bias and statistical methods which account for repeated measures on the same patients and other design features are required. Meta-analysis across cross-over trials and with parallel trials is generally problematic and more fully described in the Cochrane Handbook and other publications. For this HTA, data from parallel and cross-over trials are reported separately. There is currently no standardized, validated methodology for formal critical appraisal of cross-over trials. The criteria for risk of bias appraisal used in this HTA are

based on those described in the Cochrane Handbook and principles of epidemiology and biostatistical evaluation of correlated data and are described in Appendix D.

Meta-analyses were considered when there were two or more studies with similar patient populations, indications, interventions, control groups and outcomes. Studies on the flash CGM (FCGM) were not included in meta-analyses due to differences in device use and design and patient population. For all dichotomous outcomes, risk ratios (RR) or risk differences (RD) and their respective 95% confidence intervals (CI) were calculated to compare the rate of occurrence or relative risk between treatments. For those dichotomous outcomes (e.g proportion of responders) that could be pooled, risk ratios or risk differences and figures were produced using Review Manager v5.2.6 and the difference within each study was weighted and pooled using the Mantel-Haenszel methods. For those dichotomous outcomes that could not be pooled, RDs were calculated using the Rothman Episheet (www.krothman.org/episheet.xls*).* There is no current consensus on what constitutes a clinically meaningful change in HbA1c; thus, a value of 0.5%, which was suggested as clinically meaningful in other studies, was used in this HTA.

For continuous outcomes, the average change from baseline to follow-up for each CGM and SMBG groups was calculated. The magnitude of each group's respective change was then differenced to yield a Mean Difference (MD) as the final effect estimate. All positive MDs represent a higher degree of favorable outcomes, or effectiveness, in the SMBG group. Meanwhile, negative effect estimates correspond to a larger change from baseline in the CGM group. All continuous effect estimates were weighted and pooled according to the inverse of their variances to yield the total pooled mean difference.

In some instances, when the standard deviation was unavailable it was assumed to be the pooled average of the remaining studies within the same analysis subgroup. Furthermore, when calculating the standard deviation of the change score the correlation between baseline and follow-up measures was assumed to be 0.5. Change SD was calculated using the baseline SD (preSD) and follow-up SD (postSD) with the following formula: $\sqrt{[(preSD2 + postSD2) - (2 \times 0.5 \times preSD \times post\ SD)]}$. [65]

Careful consideration was given to the design of the trials; both parallel and crossover trials were considered. [61] While all included crossover trials applied statistical methods to account for within-patient variability, statistical methods for combining these types of trials may not fully account for attrition between periods or variation in treatment periods across studies and pooled estimates. [37] Additional steps were taken to evaluate the potential for statistical bias, where appropriate and when possible given reported data. T-tests were used to measure the correlation between treatment periods. [3] Many tests were inconclusive and therefore it was deemed appropriate to not pool across trial designs. After the validation procedures, crossover trials were combined, using similar methods as in the parallel RTCs and the change from baselines scores to calculate the MDs, however, in some instances only final follow up scores were available.

The DerSimonian and Laird random effects model was assumed to account for inter-study variability. I^2 statistics following a Chi-squared distribution were presented to show an approximated proportion of variability due to study heterogeneity not relating to sampling error. P-value of subgroup differences and test for overall difference in intervention effect was found assuming a standard normal distribution. Effect sizes were reported and displayed along with their respective 95% confidence intervals. Results and figures were produced using Review Manager v5.2.6. [127]

Outcomes not represented in the meta-analyses are detailed in the evidence tables in the appendices and/or the body of the report.

4. Results

4.1. Number of Studies Retained and Overall Quality of Studies

Overall, 28 randomized trials (in 35 publications)[14-17,19,23,39,45,48,58,64,67,69,79,81,82,88,89,91,97,113,115,121,123,125,132,138,144,147,149,150,152,154,156,163] that reported efficacy and safety outcomes were included. Additionally, 16 observational trials met inclusion criteria,[10,28,34,52,59,77,78,80,87,93,126,136,139,145,148,158] seven of which were follow-up studies/open-label phases of included RCTs (5 of the JDRF trial).[28,34,77,78,80,87,148] The selection of the studies is summarized in Table 7 below. Additionally, five economic studies were included.[29,49,70,99,131]

Table 7. Number of studies for each comparison of efficacy for included conditions.

Diabetes and age categories*	Number of studies	Studies in previous report	Studies new to report update
TYPE 1 DM			
Children	5 RCTs (8 publications)	Bergenstal 2010 (STAR 3, index trial)†	Slover 2012 (STAR 3, f/u study)
		Hirsch 2008†	Rubin 2012 (STAR 3, f/u study)
		JDRF 2008 (index trial)†	Kordonouri 2010 (ONSET trial)
		Lawrence 2010 (JDRF f/u study)†	Mauras 2012
	8 observational	Chase 2010 (JRDF subanalysis)	Kordonouri 2012 (ONSET, f/u study)
		JDRF 2009 (JDRF subanalysis)	Ludwig-Seibold 2012
		JDRF 2010 (JDRF subanalysis)	Rachmiel 2015
			Scaramuzza 2011
			Wong 2014
Adults	11 RCTs (14 publications)	Bergenstal 2010 (STAR 3, index trial)†	Beck 2017 (DIAMOND trial, index trial)
		Hirsch 2008†	Polonsky 2017 (DIAMOND trial, f/u)
		JDRF 2008 (index trial)†	Rubin 2012 (STAR 3, f/u study)
		Lawrence 2010 (JDRF f/u study)†	Hermanides 2011
			Langeland 2012‡
			Lind (GOLD trial, index study)‡
			New 2015§
			Peyrot 2009
			Tumminia 2015‡
			van Beers 2016 (IN CONTROL trial, index study)‡

Diabetes and age categories*	Number of studies	Studies in previous report	Studies new to report update
	5 observational	JDRF 2009 (JDRF subanalysis)†	Anderson 2011
		JDRF 2010 (JDRF subanalysis)†	Ludwig-Seibold 2012
			Wong 2014
Mixed (children and adults)	8 RCTs (9 publications)	Deiss 2006	Batellino 2011
		Hirsch 2008†	Batellino 2012 (SWITCH trial, index study)‡
		JDRF 2008 (index trial)†	Hommel 2014 (SWITCH trial, f/u study)‡
		JDRF 2009 (index trial)†	O'Connell 2009
			Raccah 2009
	2 observational	JDRF 2009 (JDRF subanalysis)†	
		JDRF 2010 (JDRF subanalysis)†	
TYPE 2 DM			
Adults	4 RCTs (6 publications)		Ehrhardt 2011 (index trial)
			Vigersky 2012 (f/u to Ehrhardt 2011)
			New 2015§
			Tildesley 2013 (index trial)
			Tang 2014 (f/u to Tildesley 2013)
			Yoo 2008
TYPE 1 and 2 DM, mixed			
Adults	1 RCT		New 2015§
DM with pregnancy (2 RCTs)			
Type 1 DM	1 RCT		Secher 2013
	3 observational		Cordua 2013 (subanalysis, Secher 2013)
			Fresa 2013
			Secher 2014
Type 2 DM	1 RCT		Secher 2013
Gestational	1 RCT		Wei 2016

*Some trials contributed data to more than one category.
†Data for children only from these trials was included in the previous HTA; however, because they stratified on various age groups, the indications for these studies are expanded.
‡Cross-over trial

With regard to the overall quality of retained studies, only one trial was considered to be at low risk of bias (good quality RCT)[88]; it was in children with type 1 diabetes. Half of trials (n= 14) were considered

to be at moderately high risk of bias (poor quality RCTs) while the other 14 were considered to be at moderately low risk of bias (moderate quality RCTs). Two economic studies were considered to be at moderate to good quality. Detailed descriptions of study quality are provided in Appendix E.

4.2. Key Question 1: Efficacy and Effectiveness

The number of studies retained and results regarding efficacy and effectiveness are provided below.

Primary clinical outcomes considered for evaluation of efficacy and effectiveness were:

1. Microvascular complications
2. Macrovascular complications
3. Fetal outcomes, cesarean section rates

Primary intermediate outcomes considered for evaluation of efficacy were:

1. Achieving target (i.e. age-appropriate) HgA1C level
2. Maintaining target (i.e. age-appropriate) HgA1C level
3. Acute episodes of hypoglycemia

Secondary intermediate outcomes considered for evaluation of efficacy and effectiveness were:

1. Acute episodes of hyperglycemia
2. Acute episodes of diabetic ketoacidosis
3. Quality of life (validate instruments only)

Strength of Evidence (SOE) was graded for the primary outcomes (clinical and intermediate) only.

Not all studies reported on all outcomes.

4.2.1. Type 1 Diabetes Mellitus (T1DM)

Summary of results

Few trials using newer CGM devices were identified and were in adult populations. No trials in those <18 years old using newer devices were identified. The following trials employed newer CGM technology: Beck 2017a (T1DM) Beck 2017b (T2DM), Lind 2017, van Beers 2016, Bolinder 2016 and Haak 2016.[16,17,23,58,152] Many of the trials incorporating older devices are considered pivotal trials and still provide a basis for guidelines and consensus statements. Please see Appendix J and K for detail on newer and older devices.

The general findings for T1DM for the primary clinical and intermediate outcomes are briefly summarized below by age category (children, adults, mixed population). Detailed findings (including results for secondary outcomes) are then presented. For each outcome the number of trials noted

reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. Half of the trials were moderately low risk of bias and half were moderately high risk of bias (see Appendix E). The overall strength of evidence for most efficacy outcomes was considered low across interventions and comparators. In general, if effect estimates tended to favor one treatment but failed to reach statistical significance with confidence interval crossing the null value of zero or one (perhaps due to sample size), the results are interpreted as showing no clear difference between treatments. If effect estimates are very close to zero and not statistically significant, results are interpreted as no difference between groups.

Children with T1DM

None of the trials in persons <18 years old employed newer CGM devices. Mean baseline HbA1c% in most trials was ~8%; one trial reported a value of 11.3%.

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:

HbA1C %

- Achieving HbA1c % of <7% was more common in children with CGM versus SMBG in one trial at 3 months (SOE Low) but no clear difference was seen across two trials at 6 or 12 months (SOE Moderate). Similarly, at 3 months more children using CGM had an absolute reduction in HbA1c% of ≥ 0.5% in one trial however at 6 months across two trials there was no clear difference. (SOE Low).
- CGM was not associated with clinically or statistically significant improvement in mean HbA1c across included trials. Across three parallel RCTs, a small reduction from baseline in mean HbA1c % favoring CGM over SMBG was seen at 3 months. At 6 months pooled estimates failed to reach statistical significance. At 12 months there was no clear difference between CGM and SMBG; one trial reported a clinically and statistically significant difference favoring CGM, while another did not; the pooled estimate was not statistically significant. However, one cross over trial reported a significant reduction in mean HbA1C % favoring CGM across both 6 month treatment periods. (SOE Low for 3 months, Moderate for 6 and 12 months)

Hypoglycemia

- **Severe hypoglycemic events**: Studies were likely underpowered to detect differences between treatments for this rare event, contributing to the findings of no apparent difference between CGM and SMBG with regard to the proportion of children with ≥1 severe hypoglycemic events, the number of severe events, and number of severe hypoglycemic events with seizure, coma or loss of consciousness or incidence of severe hypoglycemia at any time frame. (SOE Low)
- **Hypoglycemia (<70 mg/dL):** There were no differences between CGM and SMBG with regard to the minutes per day spent in at this hypoglycemic range or area under the curve (AUC) across two trials. (SOE Low)

- **Hypoglycemia (<55 mg/dL):** There were no differences between CGM and SMBG with regard to the minutes per day spent in at this hypoglycemic range across two trials at 3 or 6 months. (SOE Low)

Other outcomes (strength of evidence not assessed, see sections below and appendices for details)

- **Adherence:** Single arm (case series) extensions of included trials generally found that greater CGM adherence/use was associated with better HbA1c levels in children over 6 to 12 months of follow-up but no difference in time spent in hypoglycemic ranges based on adherence.
- **Quality of life and satisfaction** In general, there were no statistical differences between children who used CGM and those who performed SMBG only in self-ratings and in parent's proxy ratings across a number of generic and disease specific measures of quality of life. Hypoglycemia Avoidant Behavior scores (HFS subscale) improved more in parents of children using CGM compared with SMBG alone as well as greater satisfaction in both children and parents in the CGM versus SMBG group on Insulin Delivery System Rating Questionnaire measures in one trial. More frequent CGM use was associated with greater satisfaction among children and their parents in another trial.

Adults with T1DM

Results are for traditional CGM devices (those with automatic alarms) are reported unless otherwise noted. Results for flash CGM devices are reported separately. In most traditional CGM trials, baseline HbA1c % was >8%. The baseline HbA1c% was <7% in the single trial of flash CGM.

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:

HbA1C %

- Traditional CGM: Achieving HbA1c % of <7% was significantly more common in adults with TCGM use versus SMBG at 3, 6 across two trials and at 12 months in one trial (SOE Low at all times). Similarly, across two trials, more CGM recipients experienced an absolute HbA1c reduction of >0.5% versus SMBG (SOE Moderate) at 3 months and across two trials CGM was associated with a greater proportion of persons with a relative reduction of >10% in HbA1c than SMBG compared with baseline at 3 and 6 months (SOE Low). Across trials, the bulk of the evidence suggests clinically meaningful improvement in mean HbA1c % with CGM versus SMBG. (SOE Low) Findings from two trials of the three trials using newer devices were generally consistent (favoring CMG) to those from other trials for most HbA1c outcomes. One cross-over trial using newer devices found no difference between groups for mean A1c.
- Flash CGM: There were no differences in mean HbA1c between FCGM and SMBG at 3 or 6 months, however baseline values were <7% in both groups. (SOE Insufficient)

Hypoglycemia

- **Severe hypoglycemic events**: Studies were likely underpowered to detect differences between treatments for this rare event.
    - Traditional CGM**:** Across three parallel RCTs, there were no apparent differences between CGM and SMBG at across time points up to 12 months in the proportion of adults experiencing ≥ 1 severe hypoglycemic events or in the number of severe hypoglycemic events across 4 trials. Similarly, in one cross-over trial there was no difference in the proportion of adults experiencing ≥ 1 severe hypoglycemic event for CGM and SMBG phases after adjustment for study duration. Three of the four cross-over trials reported no difference between the phases in the numbers of events. Studies may have been underpowered to detect differences (SOE Low).
    - Flash CGM: There were no differences between FCGM and SMBG (SOE: Insufficient)
- **Hypoglycemia (<70 mg/dL):**
    - Traditional CGM: Across parallel and cross-over trials, CGM appears to be associated with decreased time spent in this range, however, the clinical significance of the effect sizes is unclear. (SOE Low) There is no clear difference between CMG and SMBG with regard to number of events standardized across days of monitoring with conflicting results between one parallel trial and one crossover trial. (SOE Low)
    - Flash CGM: FCGM was associated with decreased time spent in this hypoglycemic range and number of events compared with SMBG. (SOE: Insufficient)
- **Hypoglycemia (<55 mg/dL)**
    - Traditional CGM: As small decrease in the mean minutes per day spent in this range favoring CGM was seen at 3 months (SOE Low), but was no longer significant at 6 months (SOE Insufficient) where substantial heterogeneity was noted; results from the trial using newer devices failed to reach statistical significance.
    - Flash CGM: FCGM was associated with decreased time spent in this hypoglycemic range (SOE: Insufficient)
- **Nocturnal hypoglycemia:**
    - Traditional CGM: One parallel trial and one cross over trial suggest that the percent of time spent in hypoglycemic range of <70mg/dL at night was statistically less for CGM versus SMBG (SOE Low). Similarly in the parallel trial, the median percent of time spent in the severe hypoglycemic range (<50 mg/dL) was also less in the CGM group versus the SBMG group. (SOE Insufficient). The clinical importance of sone effect sizes is unclear.
    - Flash CGM: FCGM was associated with less time in the hypoglycemic ranges and fewer events. (SOE Insufficient).

Other outcomes (strength of evidence not assessed, see sections below and appendices for details)

- Adherence: Single arm (case series) extensions of included trials generally found that greater CGM adherence/use was associated with better HbA1c levels
- Quality of life measure and satisfaction: Results varied across various quality of life measures as reported three parallel design RCTs and two cross over trials. In general, CGM use was associated with greater improvement on the Diabetes Treatment Satisfaction Questionnaire

(DTSQ) versus SMBG across two cross-over trials, one of which used a newer device. More frequent CGM use was associated with greater satisfaction among children and their parents in an older trial. The one trial of flash CGM reported significantly improved satisfaction for FCGM versus SMBG.

Mixed populations (adults and children) with T1DM

Trials were approximately 50% children, 50% adults. None of the trials used newer devices. Baseline HbA1c% ranged from 6.4% to 9.6%.

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:

HbA1C %

- Achieving HbA1c % of <7% was significantly more common in adults with CGM use versus SMBG at 3months across 3 trials (SOE Low) but not at 6 months across 2 trials (SOE Low). Small reduction from baseline in mean HbA1c % favoring CGM was seen at 3 months (3 trials) and 6 months (4 trials), but may not be clinically important. One cross over trial also reported a reduction favoring CGM following 6 month CGM periods. (SOE Moderate at both times)

Hypoglycemia

- **Severe hypoglycemic events**: Studies were likely underpowered to detect differences. There were no differences at any time frame up to 6 months between CGM and SMBG with regard to the proportions for patients experiencing severe hypoglycemic events, the number or rates of events. Similarly, there was no difference between groups in the number of severe hypoglycemic events with seizure, coma or loss of consciousness or for events requiring intervention or assistance. (SOE Low for all outcomes)
- **Hypoglycemia (<70 mg/dL):** There were no differences in number of events, minutes/day or percent of time spent in this range between CGM and SMBG at 3 months. A 16 minute difference favoring CGM was seen across four trials at 6 months. The clinical significance of the effect size is not clear.
- **Hypoglycemia (<55 mg/dL):** There were no differences in minutes/day spent in this range between CGM and SMBG at 3 months or 6 months. (SOE Low)
- **Nocturnal hypoglycemia:** One parallel trial reported no difference between CGM and SMBG in the number of excursions below 55 mg/dL or 63 mg/dL. (SOE Insufficient)

Other outcomes (strength of evidence not assessed, see the sections below and appendices for details)

- **Adherence:** Among those using CGM, greater adherence to sensor use was associated with improved mean HbA1c at follow-up

- **Quality of life and satisfaction:** None of the included RCTs or observational studies reported quality of life in mixed populations of children and adults with T1DM.

4.2.1.1. Children with T1DM

Studies included

Studies included (RCTs)

Eight publications from five parallel trials that evaluated CGM in children with T1DM met inclusion criteria (five index publications and three follow-up publications)[19,67,81,82,88,97,132,144]. Two trials solely included people <18 years of age, while the other three included separate data on children as part of a broader sample. Sample sizes ranged from 40 to 156 participants, with the percent of male participants across trials ranging from 50% to 64%. The average age ranged from 7.5 to 12.2 year old, with the average duration of diabetes ranging from 5 to 5.8 years. Non-Hispanic white participants comprised a majority (77% to 92%) of the populations in the three trials that reported race and ethnicity. Mean baseline HbA1c values ranged from 7.9% to 11.35%. Three of these trials were industry funded.[19,67,88,132,144]

Two[19,67] of the five trials specified that additional training on pump and CGM usage was provided to the CGM intervention group, both trials exclusively used a CSII for insulin delivery. The three remaining trials did not specify additional training, in two of these trials, patients used CSII or MDI for insulin delivery and one trial exclusively used CSII. Study durations ranged from 3 months to 1 year.

Four of the five trials were rated moderately low risk of bias and one trial was rated moderately high risk of bias. Methodological concerns were primarily related to lack of independent or blind assessment across all trials. Additional concerns for the moderately high risk of bias trial were based on unclear random sequence generation and unclear allocation concealment.

One crossover trial[14] (N = 72) comparing CGM (Guardian Real-Time CGM system) to SMBG included pediatric patients with Type 1 diabetes in addition to adults (results for adults are reported elsewhere in this report). Patients ranged in age from 6 to 18 years with a mean age of 12 (SD 3.6) years in the CGM first arm and 12 (SD 3.2) years in the SMBG first arm. Forty-three percent of participants were female. Mean diabetes duration was 7.4 (SD 4.1) years for patients allocated to the CGM first arm and 6.3 (SD 3.1) years for patients allocated to the SMBG first arm. For patients allocated to the CGM first arm, mean HbA_{1c} was 8.6 (SD 0.7). For patients allocated to the SMBG first arm, mean HbA_{1c} was 8.5 (SD 0.6). The intervention periods were 6 months and the washout period between the first and second period was 4 months. During the CGM period, patients used both CGM and SMBG data to adjust treatment. During the SMBG period, patients used only SMBG data. There were no study visits during the 4 week washout period. Attrition for the entire study population, including adults and children, was 9.8%. Mean sensor use during the study was 73 percent. The trial was at moderately low risk of bias; lack of blind assessment and the failure to report first phase results were the primary methodological short comings. The trial was industry funded.

Table 8. Summary of patient characteristics for parallel and cross-over trials reporting on children with type 1 diabetes

Characteristic	Parallel Trials, n=5 (# of trials reporting/total)[19,67,82,88,97]	Battelino 2012 (cross over trial)[14]
No. males, %	50%-64% (4/5)	56.9%
Age, years; mean	7.5-12.2 (4/5)	12
Non-Hispanic white race, %	77%-92% (3/5)	NR
Total BMI, mean	20.4 (1/5)	20.5
DM duration, years; mean	5.0-5.8(2/5) *	6.8
HbA1c%, mean	7.9%-11.4% (5/5)	8.55%

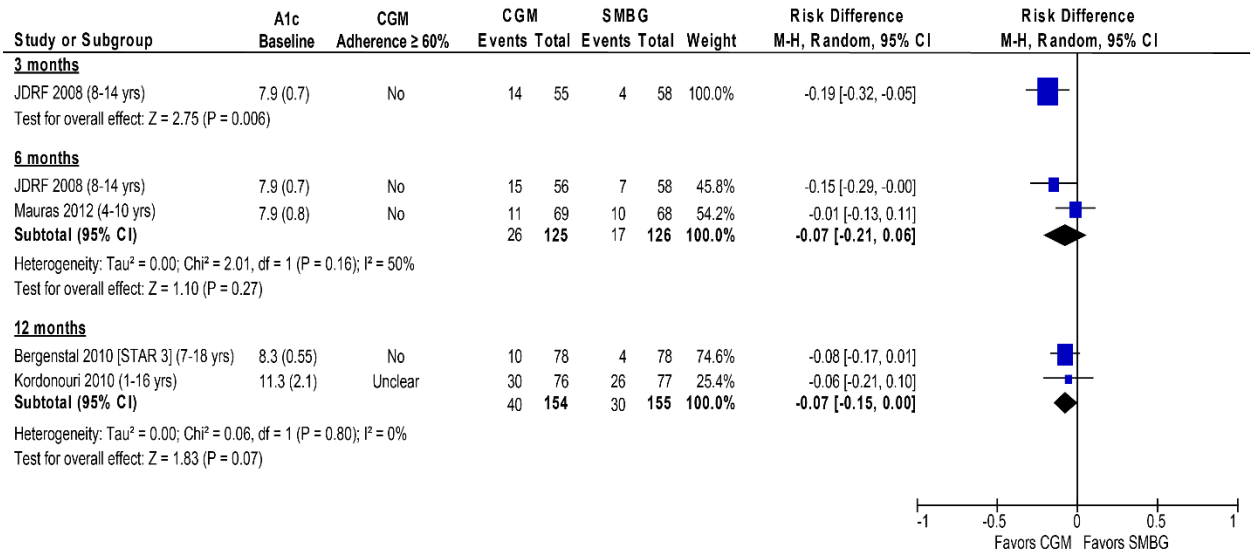
*Mauras 2012 reported a median DM duration of 3.5.

HbA1c %

Randomized controlled trials

Achieving HbA1c Target: In one parallel trial of CGM versus SMBG in children with T1DM, significantly more children in the CGM group achieved success compared with SMBG, defined as achieving HbA1C target of <7% (RD -19% 95% CI -32%to -5%)[82] however across two trials at 6 months (RD -7%, 95% CI-21% to 6%, I^2 = 50%)[82,97] and two different trials at 12 months (RD -7%, 95% CI-15% to 0%, I^2 =0%),[19,88] there was no clear differences between CGM and SMBG, Figure 3.

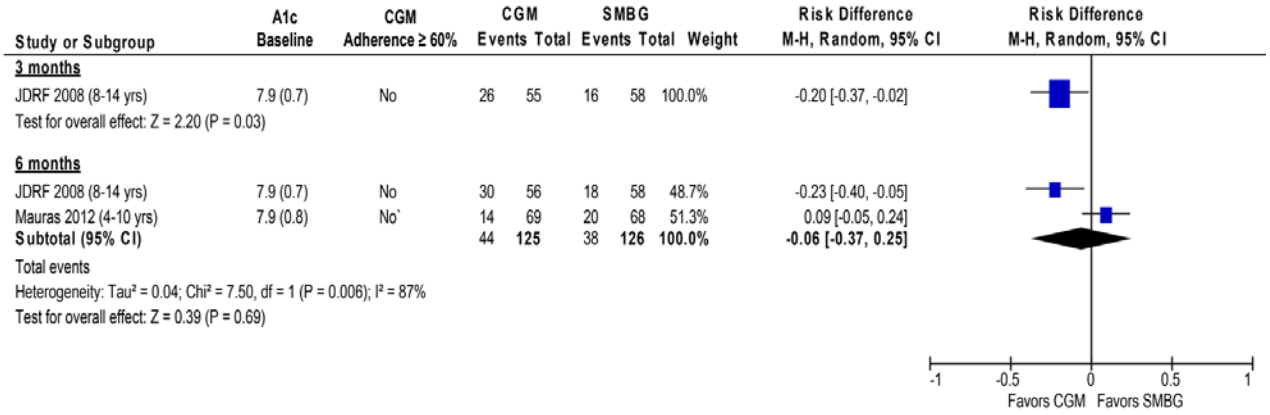
Figure 3. CMG vs. SMBG in parallel RCTs in children or adolescents: Proportion achieving HbA1c % of <7%



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; M-H: Mantel-Haenszel test; RCTs: randomized controlled trials; SMBG: self-monitoring of blood glucose; yrs: years

Absolute reduction (≥0.5% in HbA1c %) or relative reduction in HbA1c % (≥ 10% from baseline): In one parallel trial, significantly more children in the CGM group experienced an absolute reduction in HbA1c% of ≥0.5% at 3 months (RD -20%, 95% CI-37% to -2%) and at 6 months (RD -23%, 95% CI-40% to -5%). [82] By contrast, there was no difference in another trial at 6 months (RD 9%, 95% CI-6% to 24%) [97] and the pooled difference across these trials was not significant, but substantial heterogeneity was noted (RD -6%, 95% CI-37% to 25%, I^2 = 87%), Figure 4. Relative reduction in HbA1c % of ≥ 10% from baseline was only reported in the JDRF 2008 trial; more children in the CGM group experienced this at both 3 (RD -19%, 95% CI-34% to -4%) and 6 months (RD -17%, 95% CI-31% to -2%). The confidence intervals for all estimates were wide (imprecise).

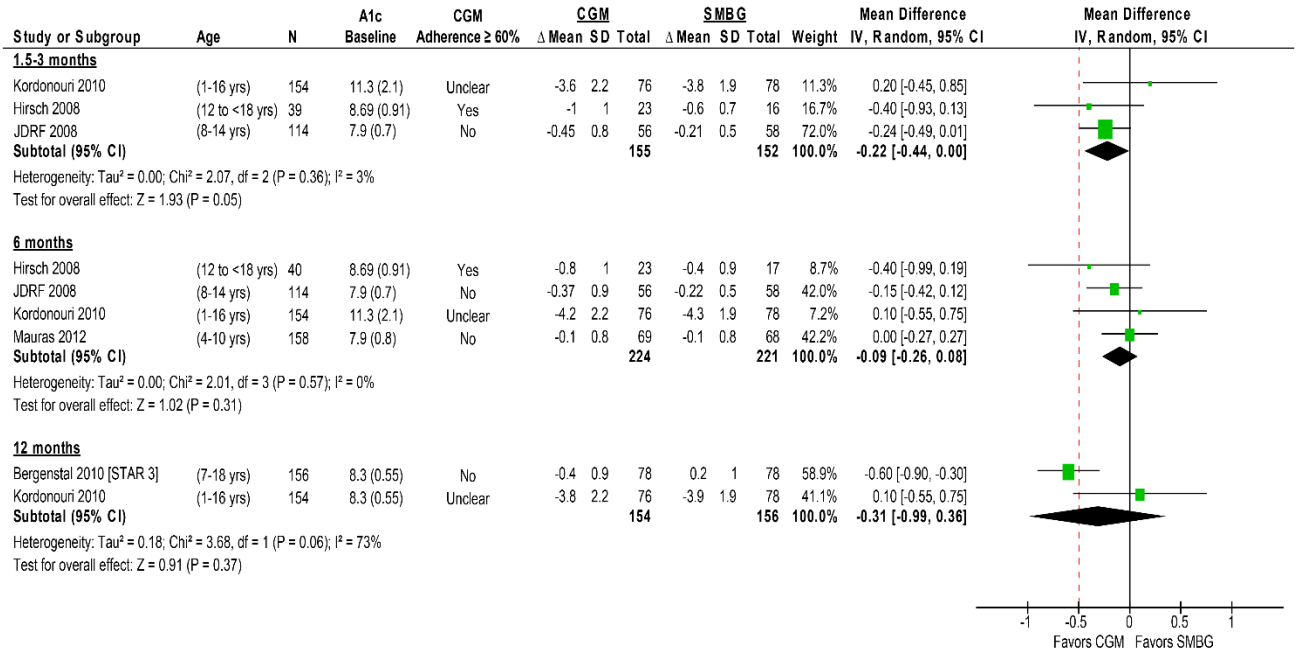
Figure 4. CMG vs. SMBG in parallel RCTs in children or adolescents: Proportion achieving an absolute reduction of ≥0.5% in HbA1c %



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; M-H: Mantel-Haenszel test; RCTs: randomized controlled trials; SMBG: self-monitoring of blood glucose; yrs: years

Change in mean HbA1c %: A small reduction from baseline mean HbA1c % favoring CGM was seen at 1.5 to 3 months but failed to reach statistical significance across three parallel design RCTs [67,82,88] compared with SMBG and may not be clinically significant (3 trials, pooled MD in change -0.22% (95% CI -0.44% to 0.0%, I^2 = 3%). (Figure 5) There was no difference between CGM and SMBG in change from baseline at 6 months (4 trials pooled MD in change scores -0.09, 95% CI-0.26 to 0.08 I^2 = 0%). [67,82,88,97] At 12 months, one trial showed a clinically and statistically significant reduction in HbA1c% favoring CGM (MD in change from baseline -0.60, 95% CI-0.90 to 0.30)[19] but not the other (0.10, 95% CI-0.55 to 0.75.[88] The pooled difference was not statistically significant across the two trials in part due to substantial heterogeneity (2 trials, pooled MD for change scores -0.31, 95% CI-0.99 to 0.36, I^2 = 73%). Reasons for the heterogeneity are not clear.

Figure 5. CMG vs. SMBG in parallel RCTs in children or adolescents: Between group difference in change from baseline in mean HbA1c%



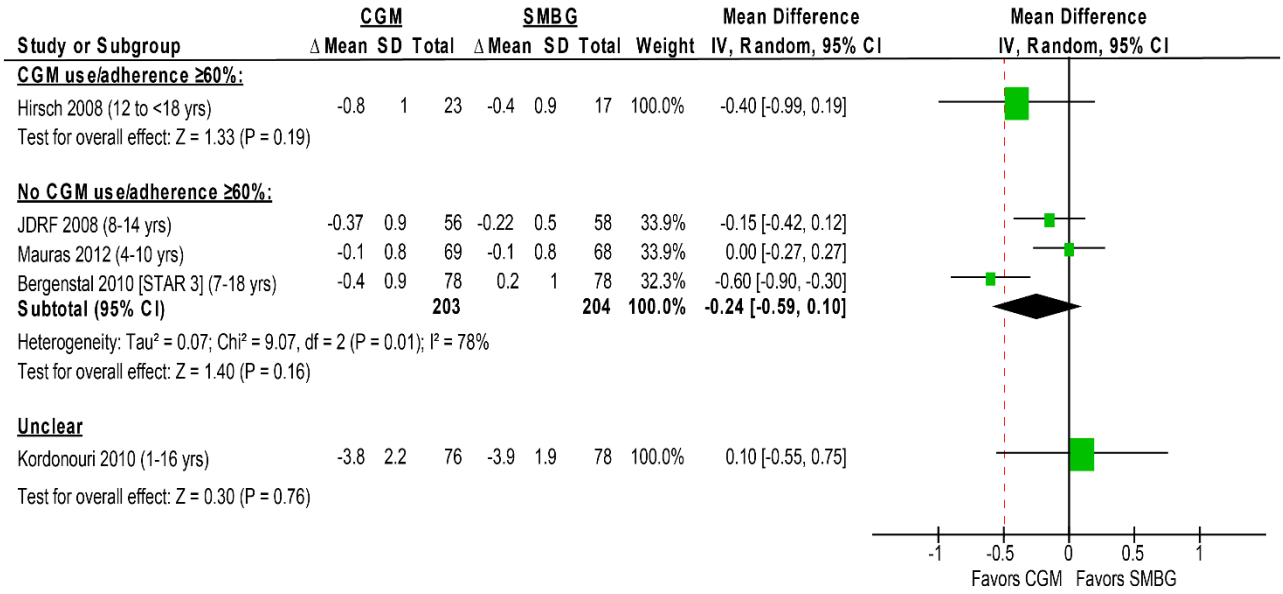
A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; M-H: Mantel-Haenszel test; RCTs: randomized controlled trials; SMBG: self-monitoring of blood glucose; yrs: years

One cross over trial at moderately low risk of bias (N = 72) reported a significant reduction in mean HbA1C % favoring CGM across both 6 month treatment periods (MD -0.46, 95% CI-0.26 to -0.66).[14] Baseline HbA1c was similar in both groups (CGM [first] 8.6 ± 0.7 vs. SMBG [first] 8.5 ± 0.6).

Adherence in RCTs

Based on our categorization of CGM use ≥60% of the time, adherence did not seem to impact differences between CGM versus SMBG in mean HbA1c % at final follow-up. However few trials reported adherence of ≥60%, Figure 6.

Figure 6. CGM vs. SMBG HbA1c % at longest follow-up stratified by CGM use of ≥60% of the time in children*



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years
*definition of use/adherence varied across trials; categorization for these analyses is provided in appendix

Among those in CGM groups only, adherence to sensor use was associated with greater improvement in mean change scores for HbA1c % in CGM patients in two trials,[88,97] but was not associated with clinically important improvement in one of them. [97] Table 9.

Table 9. Sensor adherence and mean HbA1c % values in parallel RCTs in children at follow-up

Study Follow-up *ROB*	CGM sensor adherence, definition (n)	HbA1c (%) at follow-up	P-value for difference in adherence
Kordonouri 2010 12 months *Moderately Low*	≥1 time per week (n=37)	mean 7.1 (95% CI 6.8, 7.4)	p=0.03
	<1 time per week (n=95)	mean 7.6 (95% CI 7.3, 7.9)	
Mauras 2012 6 months *Moderately Low*	≥6 days per week (n=28)	mean change -0.3 ± 0.7 reduction ≥0.5% and no severe hypoglycemia: 25% (7/28)	change scores: p=0.01 ≥0.5% reduction: p=0.33
	<6 days per week (n=41)	mean change 0 ± 0.5 reduction ≥0.5% and no severe hypoglycemia: 15% (6/41)	

CGM: continuous glucose monitoring; CI: confidence interval; HbA1c: hemoglobin A1c; RCTs: randomized controlled trials; ROB: risk of bias

Observational studies

Four of the included observational studies[87,126,136,158] reported on HbA1c levels in children using CGM versus SMBG (Table 10). One prospective cohort study[87] reported no difference in the proportion of patients achieving target HbA1c level <7.5% at 12 months (CGM 52.5% vs. 45.6%, p=0.436; RR 1.18, 95% CI 0.83 to 1.68). The two prospective cohort studies (one of which is a follow-up publication to an included RCT) [87] found no significant differences between groups in mean HbA1C % at any follow-up point (range across studies 3-24 months).[87,126] Another study (a retrospective cohort) reported significant improvement in mean HbA1c in the CGM versus the SMBG group over a mean follow-up of 18 months; the result was significant for both children (6-12 years) and adolescents (13-18 years).[136] The fourth study, a retrospective registry study, evaluated young children (<13 years) and adolescents (13 to <18 years) separately and found that CGM was associated with lower mean HbA1c levels at 12 months in the young children (8.3% vs. 8.6% with SMBG only, p<0.001) but not in the adolescents; however, the mean difference between groups for the young children was not clinically meaningful. [158]

In addition, one follow-up study of the JDRF 2008 trial[80] provided noncomparative data from children (n=47, 8–14 year olds with A1C ≥ 7%) who had been randomized initially to SMBG and were offered CGM at the end of the trial for up to 6 months. CGM use resulted in a mean increase in HbA1c of 0.2 ± 0.7% (compared to values at final follow-up from the RCT phase in this group) but the change was not statistically significant (p=0.85). The mean change in this same population from baseline to 6 months during the RCT (i.e., during SMBG only) was -0.2 ± 0.6. The proportion of children with improvement of ≥0.5% (compared with final HbA1c % at conclusion of the RCT phase) and HbA1c % levels <7.0% was 26% and 17% respectively, following 6 months of CGM use after trial termination (Appendix G).

Table 10. Comparative observational studies in children with T1DM: Mean HbA1c (%) or mean change in HbA1c (%) at follow-up

Author Study design, age range *RoB*	CGM, n	SMBG, n	F/U	HbA1c %, mean ± SD or % mean change CGM vs. SMBG	p-value
Kordonouri 2012* Pro cohort, ages 1-17 years *Moderately High*	62	69	24 mos.	7.6 ± 1.3 vs. 7.7 ± 1.2	0.493
Rachmiel 2015 Pro cohort, ages 1-17 years *High*	83	66	3 mos.	8.0 ± NR vs. 8.1 ± NR	NS
			6 mos.	7.9 ± NR vs. 8.1 ± NR	NS
			9 mos.	8.0 ± NR vs. 8.1 ± NR	NS
			12 mos.	8.0 ± NR vs. 8.1 ± NR	NS
Scaramuzza 2011 Retro cohort, ages ≤18 years *High*	129	493	Mean 18 mos.	7.4 ± 0.8 vs. 7.7 ± 1.1 change: -0.6% vs. -0.3%	0.005
	6-12 years n=NR	6-*12 years* n=NR	Mean 18 mos.	change: -0.6% vs. -0.3%	0.01
	13 to 18 years: n=NR	*13 to 18 years:* n=NR	Mean 18 mos.	change: -0.9% vs. -0.5%	<0.0001
Wong 2014 Retro registry, ages <18 years *High*	*<13 years: n*=278	*<13 years:* n=179	12 mos.	Adj.† 8.3 ± NR vs. 8.6 ± NR	<0.001
	13 to <18 years: n=4749	*13 to <18: years:* n=4676	12 mos.	Adj.† 9.0 ± NR vs. 9.0 ± NR	NS

Adj: adjusted; CGM: continuous glucose monitoring; F/U: follow-up; HbA1c: hemoglobin A1c; NR: not reported; NS: not statistically significant; Pro: prospective; Retro: retrospective; SD: standard deviation; SMBG: self-monitoring of blood glucose.

*Follow-up publication to the RCT by Kordonouri 2010 (ONSET trial); randomization was broken after 12 months; this study is considered observational.
†Linear regression model of frequency of continuous CGM use vs. HbA1c adjusted for sex, race/ethnicity, annual income, insurance status, education level, and diabetes duration.
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Adherence in observational studies

Seven observational studies explored the effect of frequency and consistency of CGM use on changes in HbA1c levels in children.[28,77,80,87,93,126,158] Four studies were follow-up studies of trials included in the previous section on RCT findings. Three of these studies were of the JDRF 2008 trial; one reported adherence to CGM use during the trial (n=56, age 8–14 years),[77] one reported continued use of CGM among those who had been randomized to CGM after the end of the trial up to 12 months (n=80, age 8–17 years)[28] and the third reported frequency of CGM use among those who had been randomized initially to SMBG who were offered CGM at the end of the trial for up to 26 weeks (n = 47, 8–14 year olds with A1C ≥ 7%).[80] The fourth subanalysis, a 24 month follow-up of the ONSET trial,[87] examined children 12 months after the end of the trial during which time they were allowed to choose how they wanted to manage their diabetes (MDI, conventional pump, or CGM); patients in the control group were offered CGM use free of charge for 3 months if they desired. The fifth cohort study (N=149) was conducted in Israel and involved five pediatric diabetes clinics (the AWeSoMe Study Group) which have experience in treating patients with real-time CGM. The prospective registry study (n=1395, age <18 years)[93] used data from the DPV (Diabetessoftware zur prospektiven Verlaufsdokumentation) diabetes documentation and quality management system in Germany and Austria and the retrospective registry study (n=9882, age <18 years)[158] used information from the T1D Exchange Clinic Network registry database which provides data on individuals with T1DM throughout the United States.

Of the five cohort studies, three (two of which were single arm follow-up studies of the JDRF 2008 trial) found that greater CGM adherence/use was associated with better HbA1c levels in children over 6 to 12 months of follow-up, regardless of the thresholds used (Table 11), however, not all changes may have been clinically significant and sample sizes for some analyses are small.[28,77,126] In one of these studies, children who used CGM consistently (≥75% of the time) also showed significant improvement when compared with the SMBG group whereas children who did not frequency showed worse HbA1c levels compared with controls.[126] Another cohort study found that HbA1c levels were lower at 24 months in those with frequent sensor use (vs. infrequent or no use) but the difference was not statistically significant (MD between groups -0.3%, p=0.236).[87] No consistent pattern for improvement in HbA1c measures was seen in the fifth cohort of SMBG patients from the JDRF trial who received CGM after trial termination (see Appendix G).[80] In both registry studies (both high risk of bias),[93,158] no significant differences between CGM adherence groups were seen, though the adjusted difference trended toward significance favoring greater CGM use in the subset of adolescents (age 13 to <18 years) in the retrospective study (Table 11).

Table 11. Frequency of CGM use and change in HbA1C % levels among children: observational studies

Study (year), Design *ROB* Outcome		Group 2	Group 3 (if applicable)	P-value
Chase 2010[28] Prospective cohort *High**	Use ≥ 6 days/week in month 12 (n = 17)	Use ≥ 6 days/week in month 6 but < 6 days/week in month 12 (n = 17)	Use < 6 days/week in both month 6 and month 12 (n = 46)	
HbA1C, % mean				<0.001†
Baseline (JDRF trial)	8.2	7.8	8.0	
6 months	7.3	7.3	8.0	
12 months	7.4	7.7	8.1	
Percent of subjects meeting target A1c‡				0.03†
Baseline (JDRF trial)	29	47	39	
6 months	65	76	35	
12 months	71	41	33	
JDRF 2009[77] Prospective cohort *High**	Average use ≥ 6 days/week in month 6 (n = 28)	Average use 4−6 days/week in month 6 (n = 21)	Average use <4 days/week in month 6 (n = 7)	
Change in HbA1c, %, age 8−14 years	−0.72§	− 0.03§	+0.02§	<0.001**
Rachmiel 2015[126] Prospective cohort *High*	Use ≥75% of the time (n=32)	Use <75% of the time (n=51)	SMBG (control) (n=66)	
Change in HbA1c % at 12 months, mean	-0.27%	+0.21	-0.04%	0.013
Kordonouri 2012[87] Prospective cohort *Moderately High*	≥ 1 sensor per week (n=33)	<1 sensor/no use per week (n=29)		
HbA1C % at 24 months, mean ± SD	7.4 ±1.0	7.7 ±1.3		0.236
Ludwig Seibold 2012[93] Prospective registry *High*	Use >30 days (n=NR)	Use <30 days (n=NR)	No CGM use (n=NR)	
HbA1C %, mean†† (follow-up NR)	8.3‡‡	8.3‡‡	8.4‡‡	NS
Wong 2014[158] Retrospective registry *High*	Average use ≥ 6 days/week	Average use 4-6 days/week	Average use <4 days/week	
HbA1C % at 12 months, mean§§				
age <13 years	7.8§§ (n=141)	8.1§§ (n=46)	8.1§§ (n=68)	0.20
age 13 to <18 years	9.2§§ (n=69)	9.1§§ (n=24)	10.3§§ (n=59)	0.05

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; NS: not statistically significant; RoB: risk of bias; SD: standard deviation; ; yrs: years

NR: not reported; SD: standard deviation

* Study was a case series; according to AAI SOP, risk of bias for case series is assessed as high

† authors report p-values from comparison across the 3 groups at 12 months (analysis of covariance for A1C, logistic regression for % meeting targets, adjusted for baseline A1c and age.

‡ A1C target was defined in this study as < 8.0% for 8−12 year olds and <7.5% for 13−17 year olds.

§ Mean values were estimated from figure 1 in article.

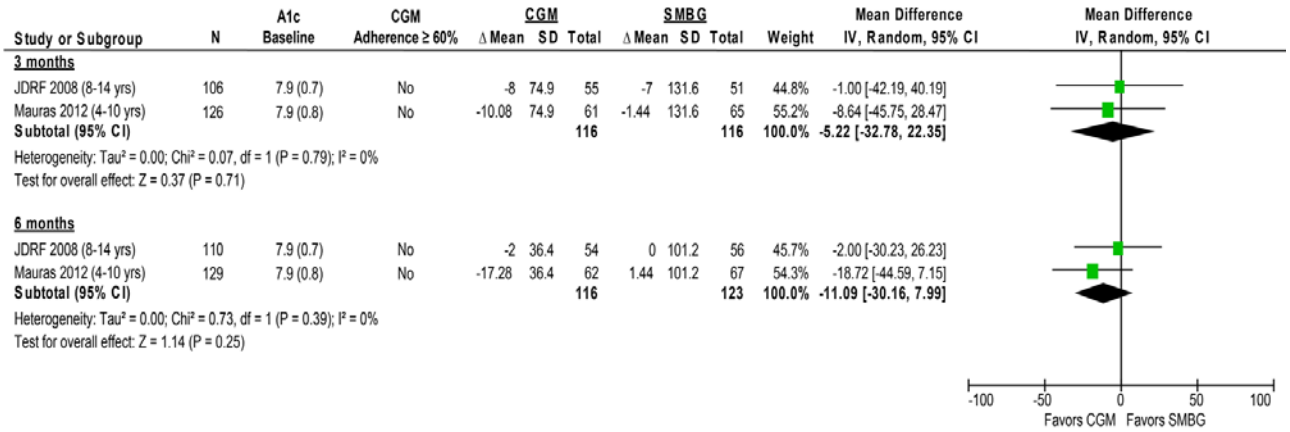
** p adjusted for baseline A1C.
†† Adjusted for age, duration of diabetes, sex, type and dose of insulin.
‡‡ Estimated from a graph.
§§ Adjusted for sex, race/ethnicity, annual income, insurance status, education level, and diabetes duration.

Hypoglycemia range ≤70 mg/dL or <50 mg/dl

Randomized controlled trials

Across parallel design RCTs, there were no differences between CGM and SMBG at any time with regard to the minutes per day spent in a hypoglycemic range of ≤70 mg/dL in two trials[82,97] (Figure 7) or with regard to area under the curve (AUC) across two trials,[19,97] Table 12. Similarly there were no differences between groups with regard to the number of minutes per day spent at ≤ 55mg/dL in two trials.[82,97]

Figure 7. CMG vs. SMBG in parallel RCTs in children or adolescents: Minutes per day in the hypoglycemia range (≤70mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Table 12. Outcomes measuring hypoglycemia in children with T1DM from parallel RCTs of CGM vs. SMBG

Author year *RoB*	Outcome	Timing	CGM Mean (SD) (n)	SMBG Mean±SD (n)	p-value
Bergenstal 2010, STAR 3 *Moderately Low*	AUC Hypoglycemia (<70 mg/dL)	Baseline	0.26 ± 0.40 (n=78)	0.23 ± 0.44 (n=81)	NR
		12 months	0.23 ± 0.41 (n=78)	0.25 ± 0.41 (n=81)	0.790
	AUC Severe Hypoglycemia (<50mg/dL)	Baseline	0.01 ± 0.04 (n=78)	0.02 ± 0.05 (n=81)	NR
		12 months	0.02 ± 0.07 (n=78)	0.01 ± 0.05 (n=81)	0.640
Mauras 2012 *Moderately Low*	AUC Hypoglycemia (<70 mg/dL)	Baseline	0.3 ± NR (n=62)	0.2 ± NR (n=67)	NR
		3 months	0.1 ± NR (n=61)	0.2 ± NR (n=65)	NR
		6 months	0.1 ± NR (n=62)	0.2 ± NR (n=67)	NR

AUC: area under curve; CGM: continuous glucose monitoring; NR: not reported; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: Type 1 Diabetes Mellitus

Observational studies

Only one of the observational studies reported on nonsevere hypoglycemia, but provided only noncomparative data. The study was a follow-up study of the JDRF 2008 trial which evaluated children (n = 44, age 8–14 years) who had been randomized initially to SMBG who were offered CGM at the end of the trial for up to 26 weeks.[81] No significant improvement from baseline (i.e., the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group) to 6 months was reported in minutes per day spent in hypoglycemic range ≤70 mg d/l (mean 56 vs. 37, respectively, p=0.61) or ≤60 mg d/l (mean 19 vs. 11, respectively, p=0.23) in children using CGM.

Adherence in observational studies

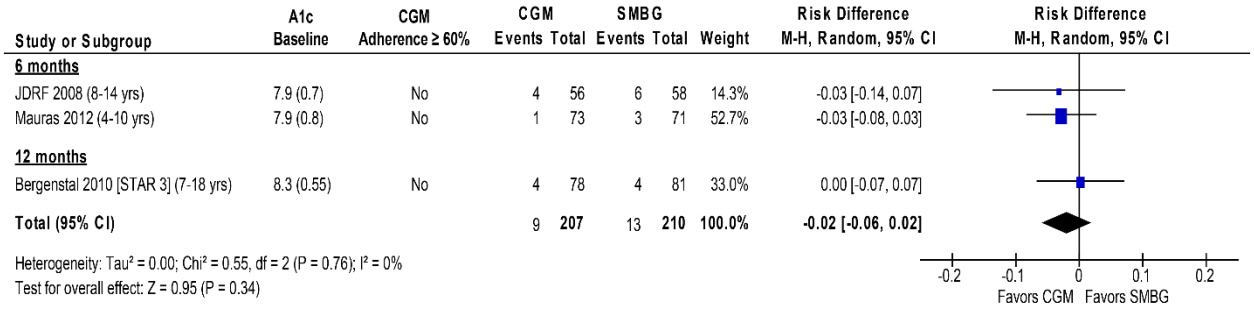
Two observational studies explored the effect of frequency and consistency of CGM use on hypoglycemia in children. One study (a follow-up analysis of the JDRF 2008 trial) which reported continued use of CGM among those who had been randomized to CGM after the end of the trial up to 12 months (n=80, age 8–17 years),[28] reported an increase from baseline in the number of minutes per day patients spent in hypoglycemic range ≤70 mg/dl for the groups using CGM at least 6 days per week in month 12 (32 vs. 19 minutes; n=17) and less than 6 days per week in both month 6 and 12 (35 vs. 30 minutes; n=29), whereas the group using CGM ≥6 days/week in month 6 but <6 days/week in month 12 (n=15) showed a decrease (43 vs. 15 minutes). The significance of these findings is unclear and the authors state that these results are difficult to interpret. However, the subjects using CGM at least 6 days per week in month 12 did show a substantial increase in time spent in the target range of 71–180mg/dL from baseline to 6 months which was sustained through 12 months (p=0.006 comparing baseline and 12 months). One prospective registry study (n=1395, age <18 years), [93] using data from the DPV (Diabetessoftware zur prospektiven Verlaufsdokumentation) diabetes documentation and quality management system in Germany and Austria, found no statistically significant difference in the rate of hypoglycemia (not otherwise specified) when comparing those who used CGM at least 30 days versus less than 30 days or no use (data not provided).

Severe Hypoglycemic events

Randomized controlled trials

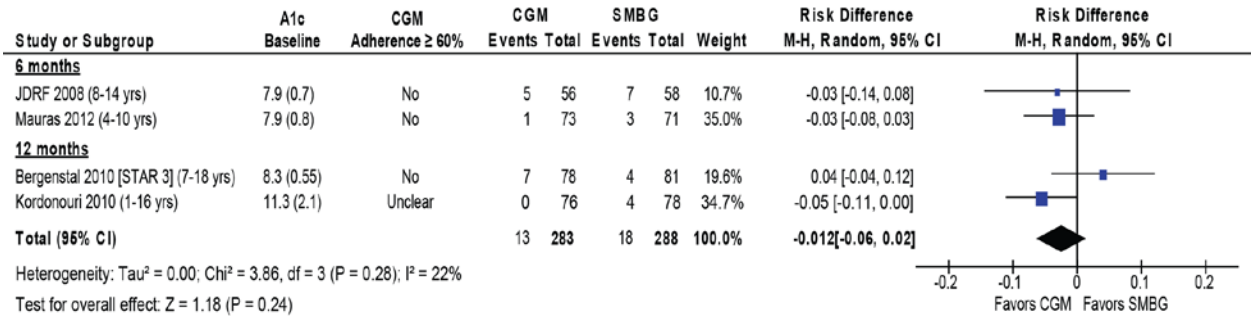
In parallel RCTs, there was no difference between CGM and SMBG with regard to the proportion of children with ≥1 severe hypoglycemic events or the number of severe events, or incidence of severe hypoglycemia; Figures 8, 9, and 10 and Table 13. Definitions used included severe hypoglycemic events with seizure, coma or loss of consciousness or those requiring assistance at any time frame. Severe hypoglycemia is a rare event and studies were likely underpowered to detect differences between treatments. Minutes per day in the hypoglycemia range were similar for CGM versus SMBG groups (Figure 11)

Figure 8. CMG vs. SMBG in parallel RCTs in children or adolescents: Proportion with ≥1 severe hypoglycemic event



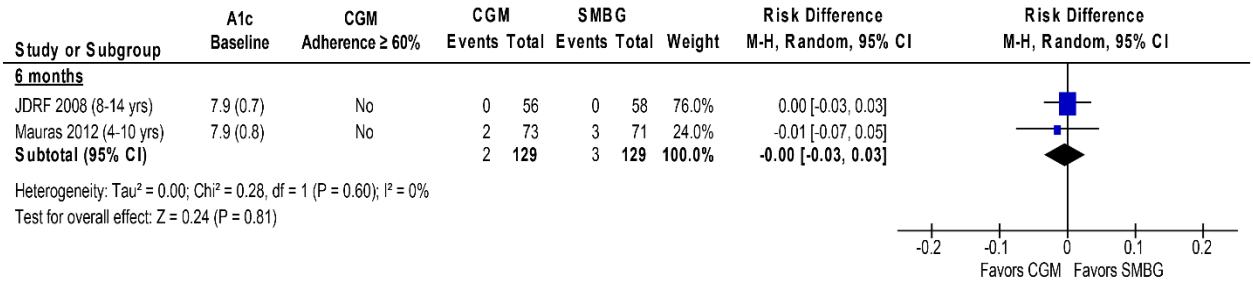
A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 9. CMG vs. SMBG in parallel RCTs in children or adolescents: Number of severe hypoglycemic events



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 10. CMG vs. SMBG in parallel RCTs in children or adolescents: Number of severe hypoglycemic events with seizure, coma or loss of consciousness



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Table 13. Parallel RCTs comparing CMG vs. SMBG in children or adolescents: Incidence of severe hypoglycemia

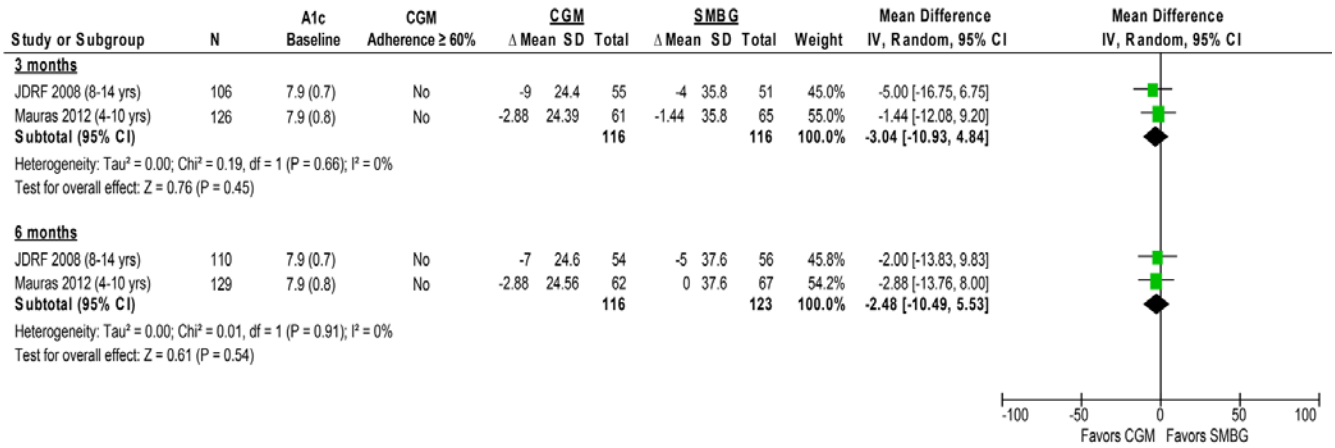
Author, Year (age range) *ROB*	Follow-up	Incidence: CGM vs. SMBG (p-value)
Severe hypoglycemic events		
JDRF 2008[82] (8-14 years) *Moderately Low*	6 months	events per 100 person years 17.9 vs. 24.4, p=0.64
Bergenstal 2010, STAR 3[19] (children 7-18 years)* *Moderately Low*	12 months	rate per 100 person years, 8.98 vs. 4.95, p=0.35
Kordonouri 2010[88] (1-16 years) *Moderately Low*	12 months	Incidence NR, p=0.46
Severe hypoglycemic events with seizure, coma or loss of consciousness		
Mauras 2012[97] (4 to <10) *Moderately Low*	6 months	rate per 100 person-years 8.6 vs. 17.6†, p=NR

CGM: continuous glucose monitoring; LOCF: last observation carried forward; NR: not reported; RCTs: randomized controlled trials; ROB: risk of bias; SMBG: self-monitoring of blood glucose; ITT: intention-to-treat

*Study used ITT using LOCF

†person years include patients who did not have coma/seizure 3 events (2 were seizure/loss of consciousness) vs. 6 events (3 were seizure/loss of consciousness)

Figure 11. CMG vs. SMBG in parallel RCTs in children or adolescents: Minute per day in hypoglycemia range (≤55mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Observational studies

There were no significant difference between the CGM and the SMBG groups in the incidence or frequency of severe hypoglycemic events across four observational studies [87,126,136,158] in children or adolescents, Table 14. The definition of severe hypoglycemia varied across the studies.

One additional observational study reported on severe hypoglycemia, but provided only noncomparative data. The study was a follow-up of the JDRF 2008 trial[80] which evaluated children (n=44, age 8–14 years) who had been randomized initially to SMBG who were offered CGM at the end of the trial for up to 26 weeks. During the 6 months post-RCT, three (5%) children experienced a severe hypoglycemic event. There were a total of four events, two of which resulted in seizure or loss of consciousness. The incidence rate was 30.8 per 100 person-years, similar to that during the control period of the RCT (30.3 per 100 person-years). No significant improvement from baseline (i.e., the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group) to 6 months was reported in minutes per day spent in hypoglycemic range ≤50 mg d/l (mean 2 vs. 1, respectively, p=0.61) in children using CGM

Table 14. Incidence or frequency of severe hypoglycemia: CMG vs. SMBG in observational studies in children or adolescents

Author, Year Study design Age range *ROB*	Definition of severe hypoglycemia	Follow-up	Incidence or frequency: CGM (n) vs. SMBG (n), treatment effect (95% CI), p-value
Kordonouri 2012* Prospective cohort Ages 1-17 years *Moderately High*	Not reported	24 mos.	0 events (n=62) vs. 1 event (n=69)†, treatment effect NR, p=NS
Rachmiel 2015 Prospective cohort Ages 1-17 years *High*	Glucose level <50 mg/dl and inability to self-treat, requiring treatment by another person	12 mos.	events per 100 person years 18.1 (n=83) vs. 10.6 (n=66), treatment effect NR, p=NS
Scaramuzza 2011 Retrospective cohort Ages ≤18 years *High‡*	Glucose level <70 mg/dL with a loss of consciousness or the patient's need for assistance.	Mean 18 mos.	events per 100 person year: 4.1 (n=129) vs. 3.9 (n=493), treatment effect NR, p=NS change from baseline in incidence: -7.8 (n=129) vs. -2.7 (n=493) events, treatment effect NR, CGM p=0.04 vs. SMBG p=NS
Wong 2014 Retrospective registry Ages <18 years *High*	Hypoglycemia (not defined further) with seizure or loss of consciousness	12 mos.	≥1 event in previous 3 months: • *<13 years*: 4% (n=278) vs. 6% (n=4,479); unadjusted OR 0.7 (95% CI 0.4 to 1.3), p=0.51; adjusted OR§ 1.0 (95% CI 0.5 to 1.9), p=0.99 • *13 to <18 years*: 9% (n=179) vs. 8% (n=4,676); unadjusted OR 1.2 (95% CI 0.7 to 2.0), p=0.51; adjusted OR§ 1.5 (95% CI 0.9 to 2.7), p=0.15

CGM: continuous glucose monitoring; CI: confidence interval; mos.: months; NS: not statistically significant; OR: odds ratio; ROB: risk of bias; SMBG: self-monitoring of blood glucose.
*Follow-up publication to the RCT by Kordonouri 2010 (ONSET trial); randomization was broken after 12 months so this study is considered observational.
†This event occurred within the second year of follow-up.
‡ Study was a case series; according to AAI SOP, risk of bias for case series is assessed as high
§Logistic regression model adjusting for sex, race/ethnicity, education level, annual household income, insurance status, duration of diabetes, HbA1c, and insulin delivery method.

Adherence in observational studies

Two observational studies, one follow-up of the JDRF 2008 trial [28] and one retrospective registry (T1D Exchange Clinic Network),[158] evaluated the effect of frequency and consistency of CGM use on severe hypoglycemic episodes in children. Neither study found an association between the frequency of CGM use and a reduction in hypoglycemic events (Table 15). Using the less than 4 days per week group as the referent, the adjusted ORs for the groups using CGM 6 or more days and 4 to 6 days were 0.8 (95% CI 0.1 to 5.9) and 1.3 (95% CI 0.1 to 17.6), respectively, for children age <13 years and 0.6 (95% CI 0.2 to

2.6) and 1.0 (95% CI 0.2 to 2.6) for children 13 to less than 18 years in the database study. In the JDRF subanalysis that reported continued use of CGM among those who had been randomized to CGM after the end of the trial up to 12 months, a total of 9 events occurred in seven children corresponding to an incidence of 11.2 events per 100 person-years.

Table 15. Frequency of CGM use and severe hypoglycemic events among children with T1DM: observational studies

Author year Design *ROB*	Group 1 % (n/N)	Group 2 % (n/N)	Group 3 % (n/N)	P-value
Chase 2010 Prospective cohort (JDRF) *High**	Use ≥ 6 days/week in month 12	Use ≥ 6 days/week in month 6 but < 6 days/week in month 12	Use < 6 days/week in both month 6 and month 12	
Frequency of severe hypoglycemic events n/N (%) , age 8-17 years	11.8% (2/17)	11.8% (2/17)	6.5% (3/46)	NS
Wong 2014 Retrospective registry *High*	Average use ≥ 6 days/week	Average use 4-6 days/week	Average use <4 days/week	
Frequency of severe hypoglycemic events n/N (%), age <13 years	5.6% (8/143)	2.1% (1/47)	4.2% (3/71)	NS
Frequency of severe hypoglycemic events n/N (%), age 13 to <18 years	5.8% (4/69)	4.0% (1/25)	10.0% (6/60)	NS

CGM: continuous glucose monitoring; NR: not reported; RoB: risk of bias; SD: standard deviation; T1DM: Type 1 Diabetes Mellitus

*Study was a case series; according to AAI SOP, risk of bias for case series is assessed as high

Nocturnal Hypoglycemia

None of the included RCTs or observational studies specifically evaluated nocturnal hypoglycemia in children treated with CGM compared with SMBG. However, noncomparative data regarding nocturnal hypoglycemia was available from one study, a follow-up of the JDRF 2008 trial [80] which evaluated children (n = 44, age 8–14 years) who had been randomized initially to SMBG who were offered CGM at the end of the trial for up to 26 weeks. The improvement from baseline to 6 months (i.e., the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group), reported in minutes per night spent in hypoglycemic range ≤70 mg d/l (mean 7 vs. 4, respectively) and ≤50 mg d/l (mean 0 vs. 0, respectively) was not statistically significant in these children using CGM (p-values not reported). Trials may not have had sufficient power to detect rare events or difference between groups for such events.

Secondary Intermediate Outcomes

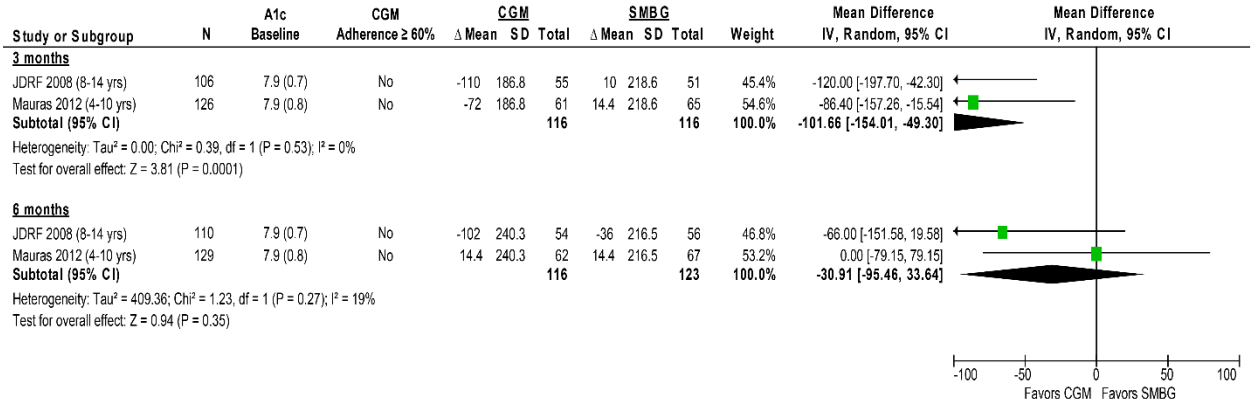
Hyperglycemia

Randomized controlled trials

Across two parallel design RCTs, results suggest that at 3 and 6 months children may have spent fewer minutes per day in a hyperglycemic range of >180mg/dL, or in a sever hyperglycemic range (<250mg/dL)

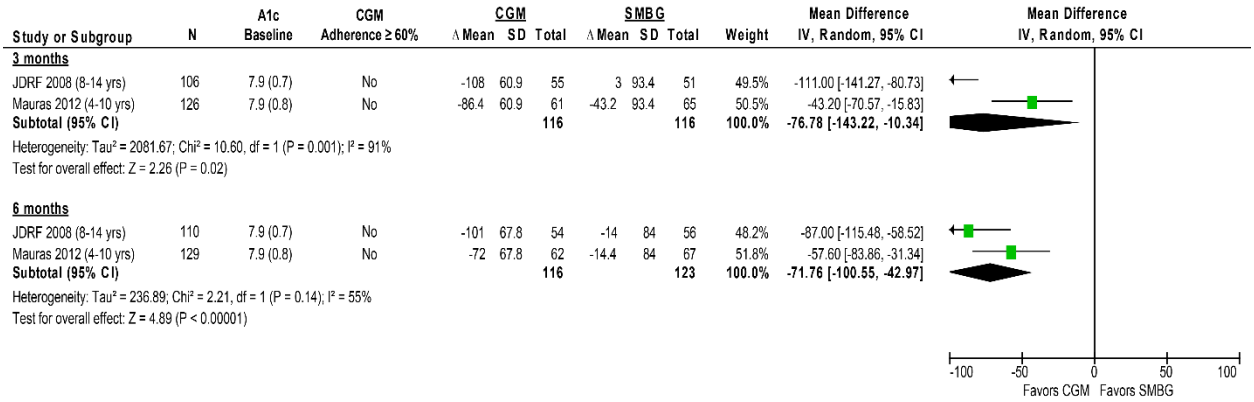
while using CGM, however, there is substantial variability in the estimates (wide confidence intervals) which suggests that estimates are not stable (Figures 12 and 13).

Figure 12. CMG vs. SMBG in parallel RCTs in children or adolescents: Minute per day in hyperglycemic range (<180 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 13. CMG vs. SMBG in parallel RCTs in children or adolescents: Minute per day in hyperglycemic range (<250 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Table 16. Outcomes measuring hyperglycemia in children with T1DM from parallel trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n)	SMBG Mean ± SD (n)
Bergenstal 2010 STAR 3 *Moderately Low*	AUC Hyperglycemia (>250 mg/dL)	Baseline	13.89 ± 11.04 (n=78)	16.23 ± 10.46 (n=81)
		12 months	9.20 ± 8.08 (n=78)	17.64 ± 14.62 (n=81)
	AUC Hyperglycemia (>180 mg/dL)	Baseline	39.36 ± 21.70 (n=78)	44.68 ± 20.34 (n=81)
		12 months	30.11 ± 17.34 (n=78)	45.29 ± 25.57 (n=81)
Mauras 2012 *Moderately Low*	AUC Hyperglycemia (>180 mg/dL)	Baseline	41 ± NR (n=62)	39 ± NR (n=67)
		3 months	32 ± NR (n=61)	33 ± NR (n=65)
		6 months	33 ± NR (n=62)	39 ± NR (n=67)

AUC: area under the curve; CGM: continuous glucose monitoring; NR: not reported; ROB: risk of bias; SD: standard deviation; SMBG: self-monitoring of blood glucose; T1DM: Type 1 Diabetes Mellitus.
* Calculated by AAI

Observational studies

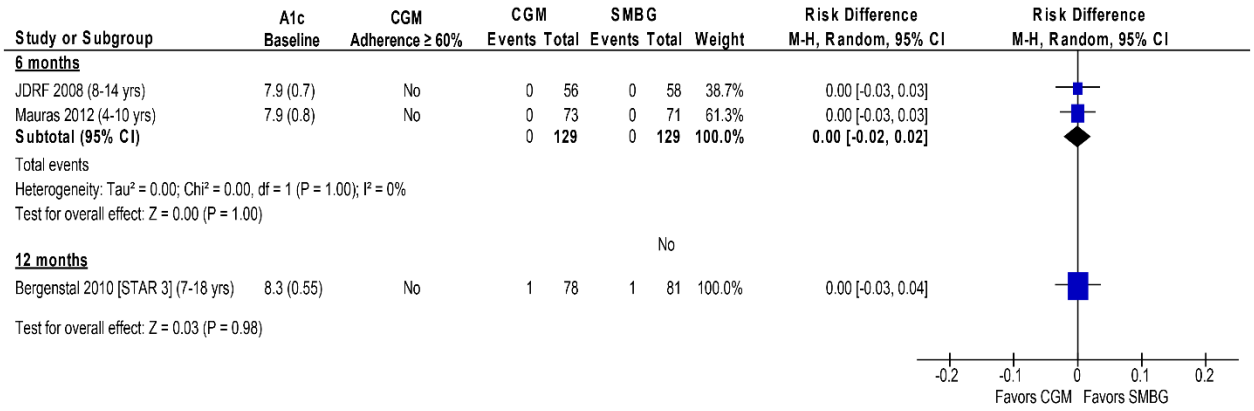
Only one of the observational studies reported on hyperglycemia, but provided only noncomparative data. The study was a follow-up of the JDRF 2008 trial [80] which evaluated children (n=44, age 8–14 years) who had been randomized initially to SMBG who were offered CGM at the end of the trial for up to 26 weeks. No significant improvement from baseline (i.e., the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group) to 6 months was reported in minutes per day spent in hyperglycemic range >180 mg/dl (mean 569 vs. 568, respectively, p=0.37) or >250 mg/dl (mean 218 vs. 193, respectively, p=0.58) in children using CGM.

Diabetic Ketoacidosis (DKA)

Randomized controlled trials

Across three parallel design RCTs, the frequency of DKA did not differ between CGM and SMBG. (Figure 14). No events occurred in either group through 6 months in two trials.[82,97] In the third trial,[19] one patient in each group (1.3% vs. 1.2%, respectively) had an episode of DKA over 12 months of follow-up; the one patient in the SMBG group had a total of two events, corresponding to a rate per 100 person years of 0.02 vs. 0.02 (p=0.20) in the CGM and SMBG groups. Studies may have lacked sufficient power to detect a difference between groups.

Figure 14. CMG vs. SMBG in parallel RCTs in children or adolescents: Frequency of DKA



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Observational studies

There were no significant differences between the CGM and the SMBG groups in the incidence or frequency of DKA events across four observational studies[87,126,136,158] in children or adolescents, Table 17. In the retrospective registry study,[158] young children (<13 years) who used CGM compared with those who did not showed a tendency toward decreased DKA frequency over 12 months; however, the difference did not reach statistical significance after adjustment. Studies may not have had sufficient power to detect differences between groups.

Table 17. Incidence or frequency of DKA: CMG vs. SMBG in observational studies in children or adolescents

Author, Year Study design (n) Age range *ROB*	Follow-up	Incidence or frequency: CGM (n) vs. SMBG (n), treatment effect (95% CI), p-value
Kordonouri 2012* Prospective cohort (n=154) Ages 1-17 years *Moderately High*	24 mos.	0 events (n=62) vs. 2 events (n=69)†, treatment effect NR, p=NS
Rachmiel 2015 Prospective cohort (n=149) Ages 1-17 years *High*	12 months	events per 100 person years 8.43 (n=83) vs. 3.03 (n=66), treatment effect NR, p=NS
Scaramuzza 2011 Retrospective cohort (n=622) Ages ≤18 years *High‡*	Mean 18 months	events per 100 person year: 0.3 (n=129) vs. 0.4 (n=493), treatment effect NR, p=NS change from baseline in incidence: -0.2 (n=129) vs. -0.1 (n=493) events, treatment effect NR, p NR (p=NS for CGM and SMBG)
Wong 2014 Retrospective registry (n=17,317)	12 months	≥1 event in previous 3 months:

Author, Year Study design (n) Age range *ROB*	Follow-up	Incidence or frequency: CGM (n) vs. SMBG (n), treatment effect (95% CI), p-value
Ages <18 years *High*		• *<13 years*: 3% (n=278) vs. 7% (n=4,749); unadjusted OR 0.4 (0.2 to 0.8), p=0.01; adjusted OR§ 0.6 (95% CI 0.3 to 1.2), p=0.13 • *13 to <18 years*: 9% (n=179) vs. 10% (n=4,676); unadjusted OR 0.9 (0.5 to 1.5), p=0.69; adjusted OR§ 1.2 (0.7 to 2.2), p=0.49

CGM: continuous glucose monitoring; CI: confidence interval; mos.: months; NR: not reported; NS: not statistically significant; OR: odds ratio; ROB: risk of bias; SMBG: self-monitoring of blood glucose.
*Follow-up publication to the RCT by Kordonouri 2010 (ONSET trial); randomization was broken after 12 months so this study is considered observational.
†These events occurred within the second year of follow-up.
‡ Study was a case series; according to AAI SOP, risk of bias for case series is evaluate as high
§Logistic regression model adjusting for sex, race/ethnicity, education level, annual household income, insurance status, duration of diabetes, HbA1c, and insulin delivery method.

Adherence in observational studies

One retrospective registry study (T1D Exchange Clinic Network)[158] evaluated the effect of frequency and consistency of CGM use on DKA episodes in children with T1DM. No association was found between the frequency of CGM use and a reduction in DKA events. In subjects less than 13 years of age who used the device 6 or more, 4 to 6, and less than 4 days per weeks, the frequency of DKA events was 2.1%, 2.1% and 2.8%, respectively (p=0.95). Using the less than 4 days per week group as the referent, the adjusted ORs for the groups using CGM 6 or more days and 4 to 6 days were 0.8 (95% CI 0.1 to 5.9) and 1.3 (95% CI 0.1 to 17.6), respectively. Corresponding values for the group age 13 to less than 18 were 5.8%, 8.0% and 10.0%; OR 0.6 (95% CI 0.2 to 2.6) and 1.0 (95% CI 0.2 to 2.6).

Health-related quality of life

Randomized controlled trials

Across three parallel design RCTs[82,88,132] there were no significant differences between children who used CGM and those who performed SMBG only in self-ratings and in parent's proxy ratings across a number of generic and disease specific measures of quality of life (KIDSCREEN-27 (1 trial),[87] Hypoglycemia Fear Survey (HFS) (2 trials),[82,132] Pediatric Quality of Life Inventory (2 trials),[82,132] and Problems Areas in Diabetes (parent version only) (1 trial)),[82] with the exception of Hypoglycemia Avoidant Behavior scores (HFS subscale) which improved more in parents of children using CGM compared with SMBG alone (change from baseline to 12 months: -4.16 vs. -1.07, respectively, p<0.01) in one trial.[132] This latter trial also reported satisfaction via the Insulin Delivery System Rating Questionnaire and noted significantly greater improvement in both children and parent's ratings in the CGM versus SMBG group on measures of Convenience, Efficacy, Overall Preference (p<0.001), and Interference and Well-being (p<0.01) (see Appendix I for details of quality of life).

One cross-over trial at moderately low risk of bias reported no difference in children's self-rating across both treatment periods using PedsQL (0-100, higher score, better quality of life), Table 18.[69] There was a statistically significant decrease in the parents' proxy rating associated with CGM use, however this was not considered to be clinically significant by the authors (see Appendix I for details).

Table 18. Summary of quality of life results from cross-over trials of CGM vs. SMBG in children with T1DM

Author year Treatment period length *ROB*	N	F/U	Outcome	Mean Difference ± SD	p-value
SWITCH **Hommel 2014** Treatment periods: 6 months Washout phase: 4 months *Moderately Low*	72	Across both treatment periods*	**PedsQL: Child's self-rating** (0-100, higher score=better quality of life)	-0.31 ± 0.84	0.712
			PedsQL: Parent's proxy rating (0-100, higher score=better quality of life)	-3.92 ± 1.18	0.002

CGM: Continuous Glucose Monitoring; F/U: follow-up; HRQOL: health related quality of life; PedsQL: Pediatric Quality of Life Inventory; ROB: risk of bias; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: Type 1 Diabetes Mellitus
*HRQOL in children and adolescents was analyzed using linear mixed models adjusted for baseline HbA1c, study period (CGM first vs. SMBG first), age group (5–7, 8–12, 13–17 years), and percentage of sensor usage. Treatment satisfaction in adults was analyzed by linear mixed models.

Observational studies

A 6-month, single arm extension study of the JDRF 2008 and 2009 trials in subjects <18 years (during which the SMBG group received a CGM device and the CGM group continued monitoring for an additional 6 months) reported that both children (n=208) and parents (n=192) were highly satisfied with CGM use as measured by the Continuous Glucose Monitoring Satisfaction Scale (CGM-SAT).[148] Overall mean scores were 3.6 ± 0.6 and 3.8 ± 0.5, respectively, out of a 0-5 scale; scores for the "benefit" and "lack of hassle" subscales were similarly high. More frequent monitoring (≥6 days/week vs. <4 days/week) was associated with higher satisfaction ($p<0.001$) for both children and parents. According to participants, the best aspects of CGM use were the ability to see trends and graphs of glucose levels, detect low glucose levels and the ability to self-correct out of range levels. Barriers to CGM use cited included alarms, issues related to insertion sites and transmitter/receiver sizes and pain with sensor insertion.

4.2.1.2. Adults with T1DM

Studies included (RCTs)

We identified seven parallel trials (ten publications) evaluating CGM in adults with type 1 diabetes mellitus that met inclusion criteria.[16,19,64,67,82,113,121] Sample sizes ranged from 28 to 339, with the percent of female patients ranging from 42% to 56.5%. The average age across trials ranged from 33 to 49 year old and the average duration of diabetes spanned 18.7 to 25 years. Two [67,121] of the seven trials reported on race and the percent of non-Hispanic white participants was 79% to 90%. BMI for study participants was similar across trials, ranging from 26.6 to 28 kg/m^2. Baseline HbA1c values ranged from 7.6% to 8.6% and all but one trial [82] reported a mean HbA1c% above 8.0%. The duration of trials ranged from 3 to 12 months.

All seven trials compared CGM to SMBG. Four[19,64,67,121] out of the seven trials exclusively used a pump modality for insulin delivery and all four specified that additional training was provided to the CGM intervention group. The three remaining studies did not specify additional training, of which two[82,113] studies used both injection and pump modalities for insulin delivery and one[16] exclusively used an injection modality. Trials based therapy modifications made during the study off of different criteria. Six different devices were used across trials, with one trial[82] using three different devices. Three of the trials [19,67,82] also included a pediatric populations, whose data are included elsewhere in this report.

Table 19. Summary of patient characteristics across six index parallel RCTs and five cross-over trials in adults with type 1 diabetes

Characteristic	Parallel trials, n=7 (# of trials reporting/total)[16,19,64,67,82,113,121]	Flash glucose (Bolinder 2016)[23]	Cross-over trials, n=5 (# of trials reporting/ total)[14,89,91,150,152]
% males	44%-58% (7/7)	57%	30%-56% (5/5)
% females	42%-57% (7/7)	43%	44%-70% (5/5)
Age, years; mean	38.3-49, 33.1* (7/7)	42, 45†	34.0-48.6 (5/5)
% non-Hispanic white race	79%-90% (2/7)	99%	99% (1/5)
Total BMI, mean	26.6-28 (5/7)	25.0	24.0-27.3 (5/5)
DM duration, years; mean	19-25 (6/7)	20‡	17.3-30.5 (5/5)
HbA1c%, mean	7.6%-8.6% (7/7)	6.7%	7.9%-8.7% (5/5)
Insulin dose, units/kg/day	NR (0/7)	D	0.5-0.7 (2/5)
% of patients with severe hypoglycemia within 12 mos (%)	10%-11% (3/7)	NR	NR (0/2)

BMI: body mass index; DM: diabetes mellitus; HbA1c: hemoglobin A1c; mos.: months; NR: not reported; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus.
*Mean age from Hirsch 2008 was not included in range because mean age included pediatric population
†42 was the median age for the CGM group, 45 was the median age for the SMBG group
‡Median duration

We identified one parallel trial evaluating flash glucose monitoring in adults with type 1 diabetes mellitus that met inclusion criteria.[23] The study randomized 241 patients into flash glucose monitoring

(n=120) using the Freestyle Libre Flash system or to SMBG (n=121) using either MDI or CSII. Out of the total patient population, 33% of the patients used CSII while the other 67% used MDI. The median age was 42 years old in the flash glucose monitoring group and 45 years old in the SMBG group. The population was 99% white and the mean BMI was 25.0 kg/m2. Baseline HbA1c was 6.7%, although the trial only included participants with an HbA1c of 7.5% or lower. The median duration of diabetes was 20 years. Prior to randomization, the trial had a two week run-in period during which patients wore a flash glucose monitor in masked mode. During the run-in period, patients who had worn the device for less than 50% of the required time were excluded from further participation of the trial. No specific training was given to the intervention group. The trial was rated as moderately high. The main methodological shortcomings were lack of concealed allocation and no blind assessment.

Five crossover trials (6 publications) compared CGM to SMBG in adult patients with Type 1 diabetes.[14,69,89,91,150,152] Table 19. Trials enrolled between 20 and 161 patients, with 10 to 82 patients allocated to CGM first and 10 to 79 patients allocated to SMBG first. Inclusion criteria varied by trial. One trial[152] enrolled patients with impaired awareness of hypoglycemia as defined by a Gold score of ≥4. Inclusion criteria for the four other trials included HbA_{1c}, ranging from greater than or equal to 7 percent to 10 percent and diabetes duration greater than one year [14,91,150] or greater than three years. [89] One trial required patients to be CGM-naïve[14] and another required patients to have either one or more hypoglycemic episodes per week or a history of at least one episode of serious hypoglycemia.[89] Three trials included patients using both MDI and CSII, [89,150,152] one trial only included patients using MDI, [91] and one trial only included patients using CSII.[14] Battelino et al.[14] included both children and adults. Most results from this trial are reported for the mixed population but results for children and adults are reported separately as available.

Participants' ages ranged from 35-49 years and 44%to 70% were female across four trials reporting on this characteristoc. In the one study that reported racial composition,[91] 99.3% of the participants were Caucasian. The mean baseline HbA_{1c} was similar across all five trials (median of trial means, 8.4%; range, 7.9% to 8.7%).

The length of the intervention ranged from 4 weeks to 6.5 months. [91] The mean duration of diabetes for the five studies ranged from 18 years[89] to 30.5 years. [152] One study used the Dexcom G4 Platinum system, [91] three used the Guardian Real-Time CGM system, [14,89,150] and one used the Paradigm Veo system with a MiniLink transmitter and the Enlite glucose sensor. [152] All five trials provided training in the use of the device either during a run-in period, [14,91,152] one month prior to the study, [150] or during the intervention period (Langeland 2012). Frequency of follow-up visits ranged from monthly [152] to every 3 months. [150] In three trials, decisions regarding medication changes were made depending on study arm. [14,89,152] During the CGM period, decisions were made using CGM data only [89,152] or using both CGM and SMBG data. [14] During the SMBG periods of these trials, decisions were made using SMBG data only. Of the remaining two trials, one provided no information about how treatment decisions were made [150] and one used only SMBG data during both periods. [91]

All five trials included washout periods. During the washout period, one trial conducted telephone consultations every 2 weeks to monitor adverse events,[152] one used only SMBG,[150] one used

conventional therapy and masked CGM for two weeks,[91] one allowed patients to monitor as individually preferred (additional detail not provided),[89] and one only specified that no study visits occurred in that period.[14] Attrition after the first phase ranged from 0%[150] to 11%[91] and overall attrition ranged from 0%[150] to 12%[91,152] among the four trials that reported attrition.

Adherence to the intervention was reported by four of the five trials as the percent of time CGM was used.[14,91,150,152] Mean usage was 87.8, 84, 89.4, and 80 percent. The fifth study[89] reported adherence in terms of "sensor days" (defined as >12 hours per day, mean was 19 sensor days).

Only one trial was considered at moderately low risk of bias[14,69 91,152]; the remaining four were moderately high risk of bias.[89,91,150,152] Common methodological concerns across trials included lack of blind assessment, no details regarding handling of missing data, no intent to treat analysis, no concealed allocation, and no analysis of carryover effect. In addition, Tumminia et al.[150] only reported data for patients with >40% sensor use. None of the cross-over trials reported data after the first treatment period only precluding comparison between the first and second treatment periods.

Primary Intermediate Outcomes

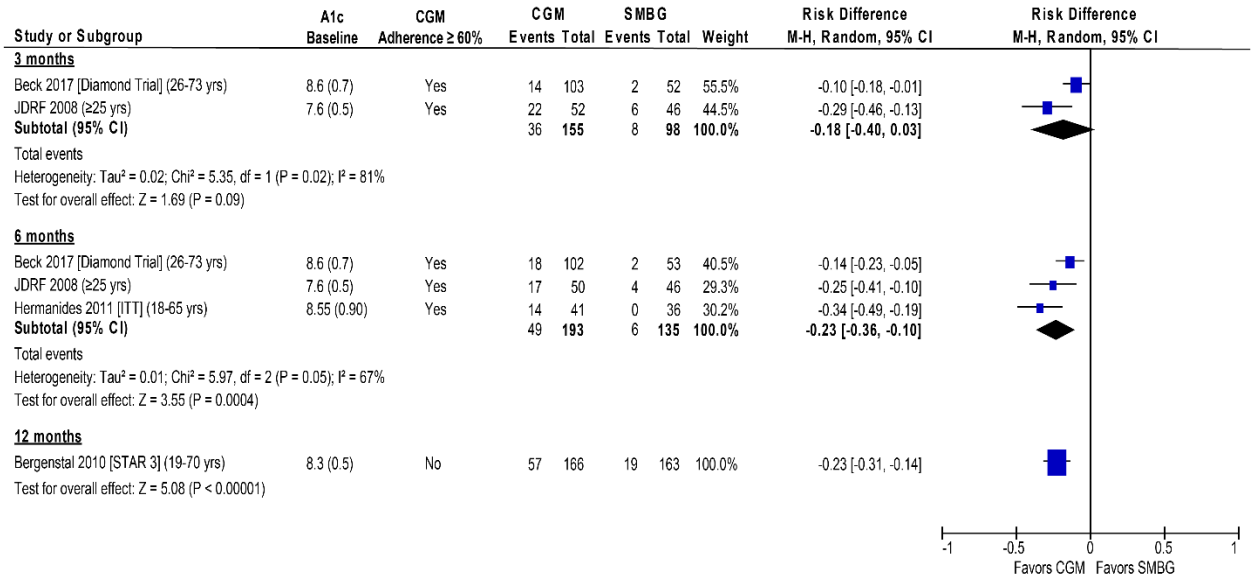
Results are presented for traditional CGM monitors then for the FCGM. In all unlabeled results CGM refers to traditional CGM devices unless otherwise noted.

HbA1c %

Randomized controlled trials

Achieving HbA1c Target: More adults in the CGM group achieved success compared with SMBG, defined as achieving HbA1C target of <7% across time frames, Figure 15. Results did not reach statistical significance at 3 months, however (2 trials, pooled RD -18%, 95% CI-40% to 3.0%, I^2 = 81%)[16,82]; although substantial heterogeneity was noted, effect estimates for both trials favored CGM and the largest trial[16] reached statistical significance. Similarly at 6 months, more adults in the CMG group versus the SMBG group achieved the target (3 trials pooled RD -23%, 95% CI-36% to -10%, I^2 = 67%); again all point estimates favored CGM.[16,64,82] A single trial reported similar results at 12 months (RD -23%, 95% CI-31% to -14%).

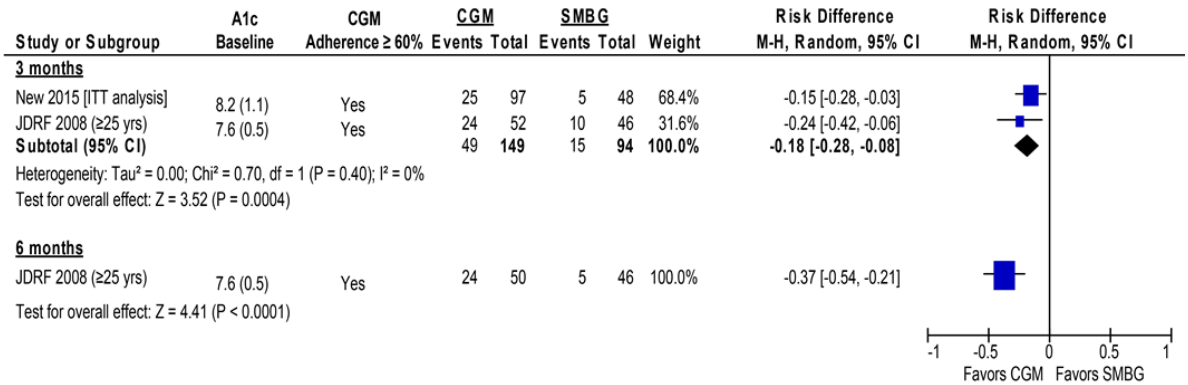
Figure 15. CMG vs. SMBG in parallel RCTs in adults: Proportion achieving HbA1c % of <7%



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

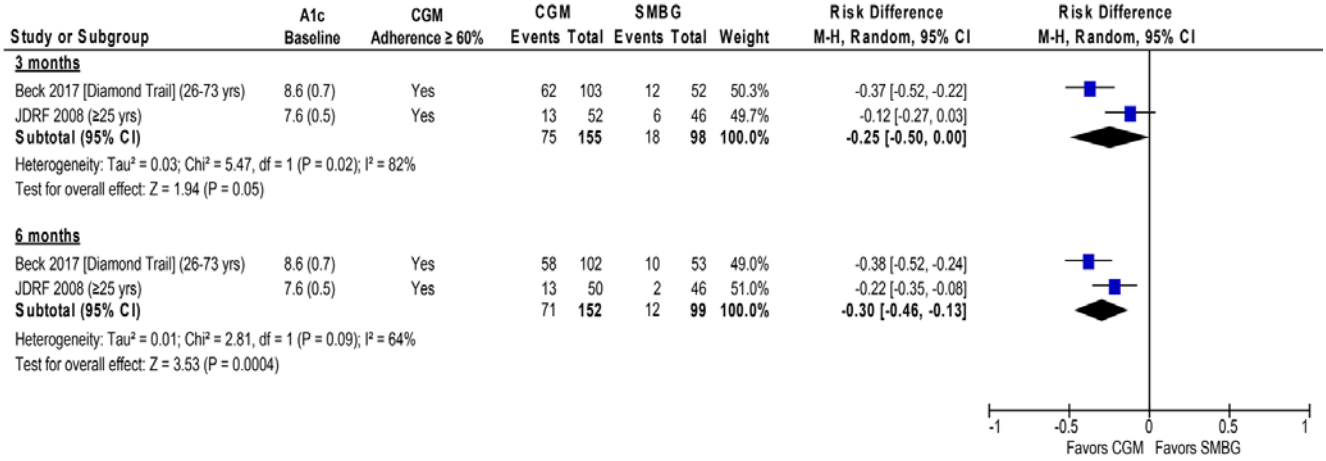
Absolute reduction (≥0.5% in HbA1c %) or relative reduction in HbA1c % (≥ 10% from baseline): Across two trials, significantly more CGM recipients than those performing SMBG experienced an absolute HbA1c reduction of >0.5% at 3 months (pooled RD -18%, 95% CI-28% to -8%, I^2=0%) (Figure 16).[82,113] The effect appeared to persist to 6 months (RD -37%, 95% CI -54% to -21%) in the one trial reporting at time.[82] Confidence intervals are wide for all estimate. Two trials[16,82] reported more adults in the CGM group experienced a relative reduction of >10% in HbA1c relative to baseline at 3 months (2 trials, pooled RD -25% , 95CI -50% to 0%, I^2=82%) with the largest, most recent trial[16] reaching statistical significance. Pooled estimates at 6 months across these trials were statistically significant (2 trials, pooled RD -30%, 95% CI-46% to -13%, I^2=64%) (Figure 17).

Figure 16. CMG vs. SMBG from parallel RCTs in adults: Proportion achieving absolute HbA1c reduction of ≥0.5% from baseline



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 17. CMG vs. SMBG in parallel RCTs in adults: Proportion achieving relative reduction >10% from baseline



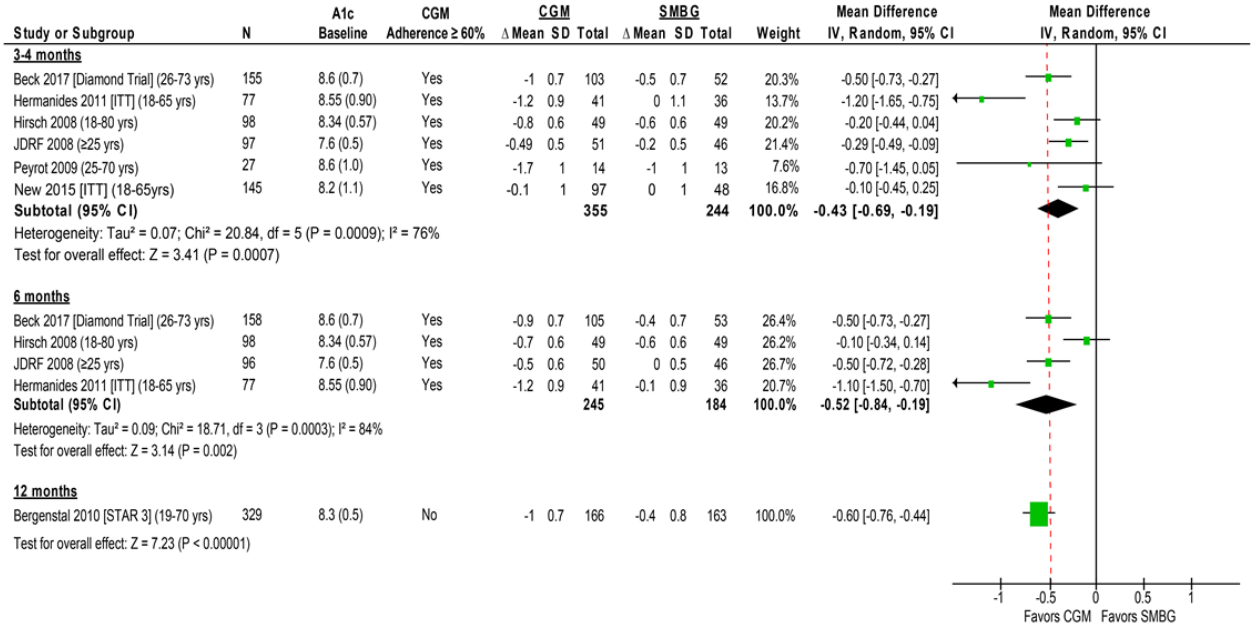
A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Between group change in mean HbA1c % from baseline:

Parallel trials

CGM use was associated with clinically meaningful and statistically significant mean between group difference in how HbA1c changed from baseline and 3-4 months (6 trials, pooled mean difference in change scores was -0.43%, 95% CI-0.69% to -0.19%, I^2=76%),[16,64,67,82,113,121] 6 months (4 trials , mean difference in change scores -0.52%, 95% CI -0.84% to -0.19%, I^2=84%)[16,64,67,82] and 12 months (1 trial, -0.60%, 95% CI -0.76% to -0.44%),[19] Figure 18. Unexplained heterogeneity was noted at 3-4 months and 6 months. Most trials were at moderately low risk of bias; one was a small, poor quality RCT.[121]

Figure 18. CMG vs. SMBG in parallel RCTs in adults: Between group difference in HbA1c % change from baseline



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

One trial of FCGM in participants with well-controlled T1DM reported no difference in mean HbA1c at 3 or 6 months or in the difference in change from baseline at either time period.[23] The MD in change scores at both times was 0%, 95 CI -0.17% to 0.17%.

Cross over trials and interpretation relative to parallel trials

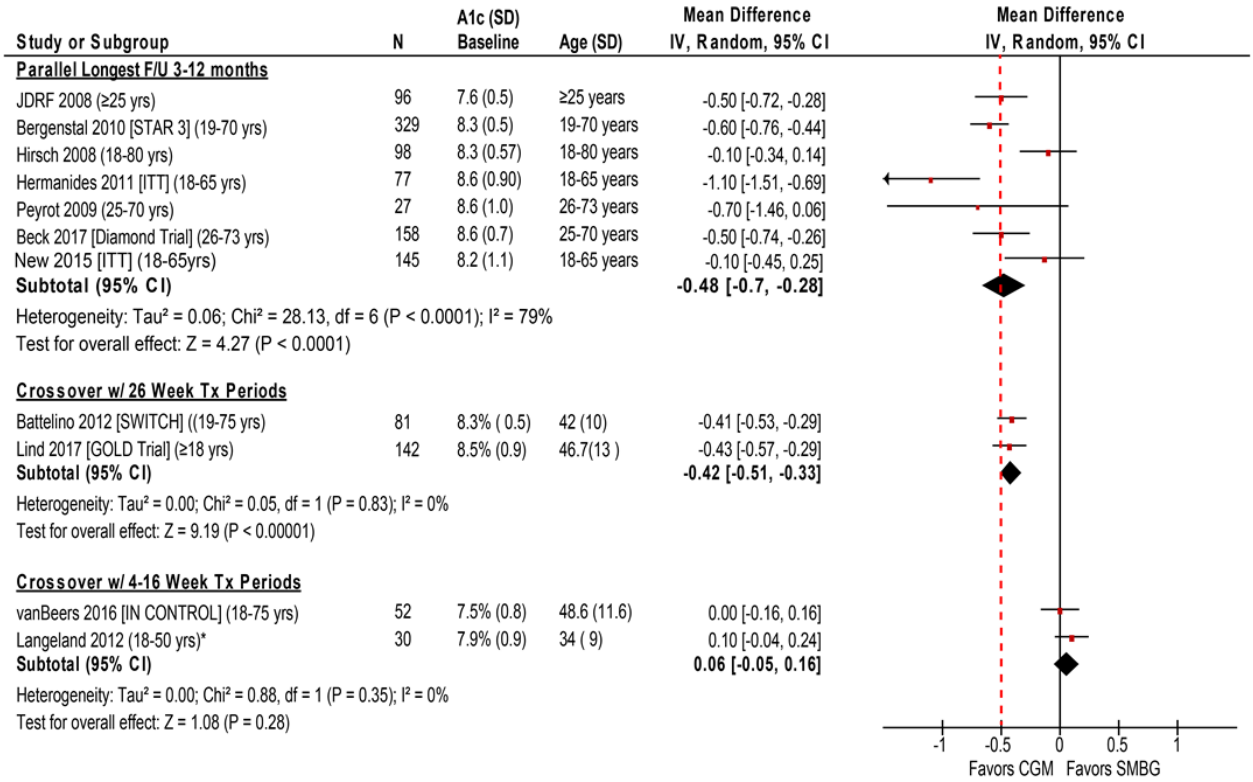
Across parallel trials at the longest follow-up (range 3 months to 12 months), CGM was associated with a clinically meaningful and statistically significant reduction in mean HbA1c % compared with SMBG (7 trials, pooled MD -0.48, 95% CI -0.70 to -0.28, I^2=79%)[16,19,64,67,82,113,121] (Figure 19) however substantial heterogeneity and lack of precision are noted.

Although the included cross-over trials did use statistical methods to account for within-patient variability, statistical methods for combining these types of trials may not fully account for attrition between periods or variation in treatment periods across studies and pooled estimates across cross-over trials should be interpreted cautiously.[46,65,114] The pooled mean difference across four cross-over trials failed to reach statistical significance, due to substantial heterogeneity (I^2 = 94%) potentially related to difference in the trials with regard to intervention protocols and/or baseline A1c. The two largest trials (moderately low risk of bias) were similar with regard to treatment period (6 months), washout periods (16-17 weeks) and mean baseline A1c (8.3% and 8.4%).[14,91] Findings from these trials were consistent and the pooled estimate suggests a significant improvement in HbA1c % favoring CGM (2 trials, pooled mean difference -0.42, 95% CI -0.51 to -0.33, I^2 = 0%), Figure 19. These findings are also largely consistent with the findings from the parallel RCTS. By comparison, the other two trials had shorter treatment periods (4 weeks and 16 weeks) and lower baseline A1C values (7.5% and 7.9%,

pooled mean difference 0.06, 95% CI-0.05 to 0.16, I^2 = 0%).[89,152] Further, baseline differences in A1c between those receiving CGM first and SMBG first in one of these trials (moderately high risk of bias) (8.1% vs. 7.6%) likely biased end of period results.[89] One trial at moderately high risk of bias, which was excluded from meta-analysis as authors only reported results among individuals who reported >40% CGM use, reported no difference between CMG and SMBG periods (mean difference -0.02, 95% CI -0.22 to 0.18).[150] The comparison between the parallel and cross-over trials is qualitative and indirect. The majority of trials were at moderately low risk of bias, exceptions being Hirsch 2008, Peyrot 2009 and Langeland 2012 which were considered at moderately high risk of bias. Peyrot 2009 and Langeland 2012 were small RCTs.

The comparison between the parallel and cross-over trials is qualitative and indirect and should be interpreted cautiously. The majority of trials were at moderately low risk of bias, exceptions being Hirsch 2008, Peyrot 2009 and Langeland 2012 which were considered at moderately high risk of bias. Peyrot 2009 and Langeland 2012 were small RCTs.

Figure 19. CMG vs. SMBG parallel and cross-over RCTs in adults: Mean difference in HbA1c at longest follow-up or treatment period



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

*Langeland 2012 (moderately high risk of bias): Baseline differences in A1c between those receiving CGM first and SMBG first 8.1% vs. 7.6%

Adherence

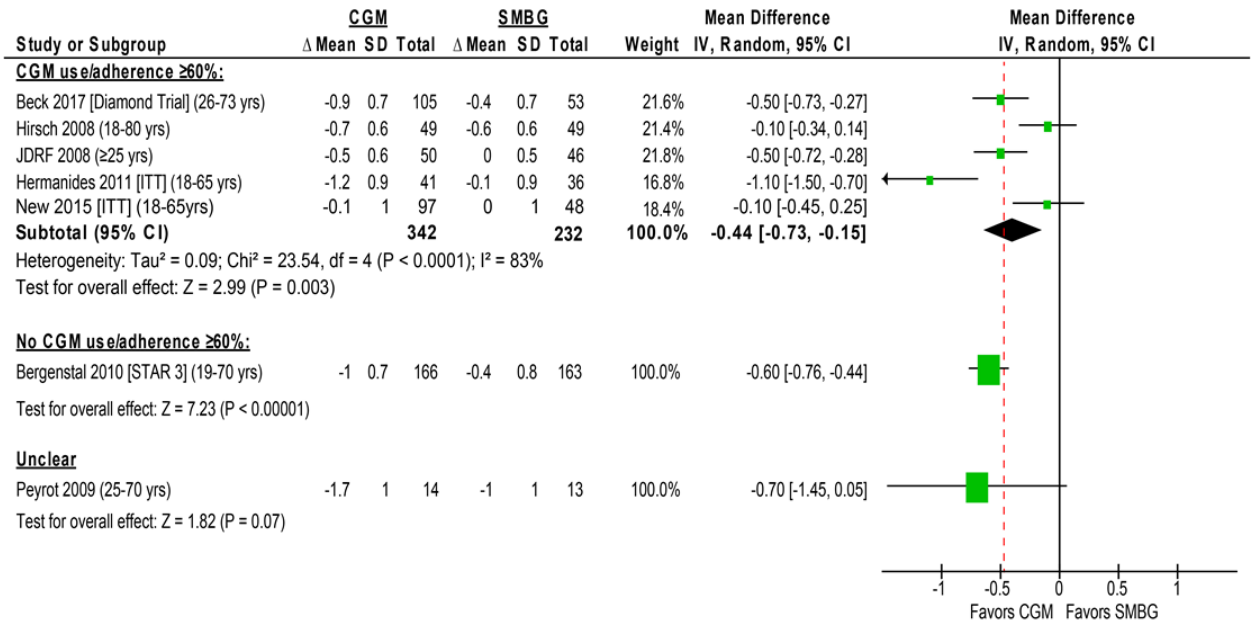
Among those in the CGM group only, sensor use of >60% of the time was not associated with significant reduction in mean HbA1c % in one parallel trial.[64] No difference between the CGM phases and SMBG phases in mean change in Hba1c % from baseline for those using sensors >70% of the time versus <70% of the time were seen in one cross-over trial.[91] Another small, poor-quality cross-over trial reported that in those using sensors ≥40% of the time during the CGM phase, there was a statistically significant decrease in HbA1c % while there was a statistically significant increase in mean change from baseline in those using sensors <40% of the time during the CGM phase, [150] Table 20. Based on our categorization of use of ≥60% of the time, adherence did not seem to impact differences between CGM versus SMBG in mean HbA1c % at final follow-up,[16,19,64,67,82,113,121] however few trials reported adherence of <60% and comparison is qualitative (Figure 20).

Table 20. Sensor adherence and HbA1c % values in parallel RCTs and cross-over trials in adults at follow-up

Study Follow-up, study type *ROB*	CGM sensor adherence (n)	HbA1c (%) at follow-up, mean change (95% CI) or mean change ± SD	p-value
Hermanides 2011 6 months, RCT *Moderately Low*	>60% of the time (n=56)	NR	No relationship between sensor use and reduction in HbA1c (adjusted for baseline values); regression coefficient 0.006, p=0.20
	<60% of the time (n=15)	NR	
Lind 2017 6 months, cross-over trial *Moderately High*	>70% of the time (n=NR)	mean change -0.46 (95% CI 0.31, 0.61)	p=NR for between group difference
	<70% of the time (n=NR)	NR (p=NS)	
Tumminia 2015 6 months, cross-over trial *Moderately High*	≥40% of the time (n=14)	CGM phase: mean change -0.78 ± 0.4 SMBG phase: mean change -0.14 ± 0.5	CGM phase: p<0.05 SMBG phase: p=0.20
	<40% of the time (n=6)	CGM phase: mean change 0.31 ± 0.6 SMBG phase: NR	CGM phase: p<0.05

CGM: continuous glucose monitoring; CI: confidence interval; HbA1c: hemoglobin A1c; NR: not reported; NS: not statistically significant; SMBG: self-monitoring of blood glucose.

Figure 20. CGM vs. SMBG HbA1c % at longest follow-up stratified by CGM use of ≥60% of the time in adults*



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

*definition of use/adherence varied across trials; categorization for these analyses is provided in appendix

Observational studies

Three observational studies, one prospective cohort study,[145] one retrospective database study[10] and one retrospective registry study,[158] reported HbA1c levels in adults with T1DM using CGM versus SMBG.

The prospective cohort study[145] compared 27 CGM users (DexCom G4 and Enlite sensor devices) with 18 SMBG patients over the course of 12 months. Mean patient age was 36 ± 13 years and mean baseline HbA1c% was 8.3% ± 0.9%. Significantly more patients using CGM versus SMBG achieved a target HbAc1 level of <7.0% at final follow-up: 48% vs. 18%; risk difference 30% (95% CI 4% to 57%), p=0.04. Patients using CGM also had statistically and clinically lower mean HbA1c % levels at 12 months compared with those conducting SMBG: mean difference -0.91% (95% CI -1.47% to -0.35%), p=0.002; this difference was significant starting around month 3.

One retrospective database study compared two CGM groups, a long-term use group (CGM use ≥3 months) and a short-term use group (CGM use <3 months), with two matched control groups of non-CGM users and found that patients in the long-term CGM group (mean 1.1 years of use) showed significant improvement in HbA1c compared with long-term controls (adjusted MD -0.76, 95% CI -1.17 to -0.33), Table 21. [10] There was no difference between the short-term use CGM (mean 33 days of use) and matched control groups.

One retrospectively registry study evaluated young adults (18 to <26 years) and adults (≥26 years) separately and found that CGM was associated with lower HbA1c levels at 12 months in those ≥26 years (7.7% vs. 7.9%) but not in the young adults (Table 21).[158]

Table 21. Comparative observational studies in adults with T1DM: HbA1c (%) at follow-up

Author Study design Age range *ROB*	Strata	CGM, n	SMBG, n	F/U	HbA1c % CGM vs. SMBG, MD (95% CI) or mean ± SD	p-value
Anderson 2011 Retrospective database Age 17-87 years *High*	Long-term (≥3 mos.) CGM use*	34†	408	Mean 12 mos.	Adj.‡ MD -0.76 (95% CI -1.17, -0.33)	<0.001
	Short-term (<3 mos.) CGM use*	43†	1204	Mean 30 mos.	Adj.‡ MD -0.22 (95% CI -0.55, 0.10)	0.19
Wong 2014 Retrospective registry Ages ≥18 years *High*	Age 18 to <26 years	157	2612	12 mos.	Adj.§ mean 8.4 ± NR vs. 8.5 ± NR	0.33
	Age ≥26 years	999	3667	12 mos.	Adj.§ mean 7.7 ± NR vs. 7.9 ± NR	<0.001

Adj: adjusted; CGM: continuous glucose monitoring; F/U: follow-up; HbA1c: hemoglobin A1c; MD: mean difference; mos.: months; NR: not reported; SD: standard deviation; SMBG: self-monitoring of blood glucose; T1DM: Type 1 Diabetes Mellitus.
*Control groups were matched to the CGM groups with respect to CGM start date and the date for the last HbA1c value after 3 months.
†Patients having used both short-term (as first therapy) and long-term CGM therapy were included in both study groups; there were a total of 8 patient who met this criteria.
‡Adjusted for insulin regimen and insulin dose
§Linear regression model of frequency of continuous CGM use vs. HbA1c adjusted for sex, race/ethnicity, annual income, insurance status, education level, and diabetes duration.

In addition, one follow-up study of the JDRF 2008 trial,[80] which evaluated adults (n=51, age ≥24 years, with A1C ≥ 7%) who had been randomized initially to SMBG and who were offered CGM at the end of the trial for up to 26 weeks, reported HbA1c results. Noncomparative data only were available. A significant reduction was seen in HbA1c from baseline, -0.4 ± 0.5%, p=<0.001 (baseline refers to the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group). The mean change in this same adult population from baseline to 6 months during the RCT (i.e., during SMBG only) was +0.2 ± 0.5. The proportion of adults with improvement of ≥0.5% and HbA1c % levels <7.0% was 45% and 29% respectively, following 6 months of CGM use after trial termination.

Adherence in observational studies

Four observational studies explored the effect of frequency and consistency of CGM use on changes in HbA1c levels in adults. The two prospective studies consisted of follow-up studies of the JDRF 2008 trial; one reported adherence to CGM use during the trial (n=50, age ≥25 years)[77] and the other reported frequency of CGM use among those who had been randomized initially to SMBG who were then offered CGM at the end of the trial for up to 26 weeks (n=51, age ≥25 years with A1C ≥ 7%). [80] One prospective database study (n=1479, age >18 years)[93] used data from the DPV system in Germany and Austria and a retrospective registry study (n=7435, age ≥18 years)[158] used information from the T1D Exchange Clinic Network in the United States. All four studies found that greater CGM adherence/use was associated

with better HbA1c levels in adults over 6 to 12 months of follow-up, regardless of the thresholds used, with the exception of patients between the ages of 18 and 26 years in the retrospective database (Table 22). One of the JDRF extension studies also reported the proportion of patients that improved HbA1c by ≥0.5% and who had levels <7% with better results seen for those with greater CGM adherence/use (Appendix Table X).[28,77,126]

Table 22. Frequency of CGM use and change in HbA1C % levels among adults: observational studies

Author year Design *ROB* Outcome, f/u, age range	Group 1 Mean ± SD (n)	Group 2 Mean ± SD (n)	Group 3 Mean ± SD (n)	Group 4 (if applicable) Mean ± SD (n)	P-value
JDRF 2010 Prospective cohort *High**	Average use ≥ 6 days/week	Average use 4−6 days/week	Average use >0 to <4 days/ week	Average use 0 days/week	
Change in HbA1c %, 6 months, age ≥25 years	−0.4 ± 0.4 (n=37)	−0.5 ± 0.3 (n=6)	−0.4 ± 0.7 (n=4)	+0.1 ± 0.9 (n=4)	0.01
JDRF 2009 Prospective cohort *High**	Average use ≥ 6 days/week	Average use 4−6 days/week	Average use <4 days/week		
Change in HbA1c %, 6 months, age ≥25 years	−0.54† ± NR (n=43)	−0.38† ± NR (n=6)	+0.01† ± NR (n=1)		0.02‡
Ludwig Seibold 2012 Prospective registry *High*	Use >30 days (n=NR)	Use <30 days (n=NR)	No CGM use (n=NR)		
HbA1C % §, F/U NR, age >18 years	7.3† ± NR (n=NR)	8.0† ± NR (n=NR)	8.0† ± NR (n=NR)		0.036
Wong 2014 Retrospective registry *High*	Average use ≥ 6 days/week	Average use 4-6 days/week	Average use <4 days/week		
HbA1C %**,12 months, age 18 to <26 year age ≥26 years	 8.6†± NR (n=49) 7.0 ± NR (n=543)	 8.5†± NR (n=32) 7.3 ± NR (n=149)	 8.6†± NR (n=52) 7.3 ± NR (n=205)		 0.88 <0.001**

CGM: continuous glucose monitoring; F/U: follow-up; HbA1c: hemoglobin A1c; NR: not reported; SD: standard deviation
*Study was a case series; risk of bias is assessed as high for case series according to AAI SOP
†Mean values were estimated from figure in article.
‡Adjusted for baseline A1C.
§Adjusted for age, duration of diabetes, sex, type and dose of insulin.
**Adjusted for sex, race/ethnicity, annual income, insurance status, education level, and diabetes duration.

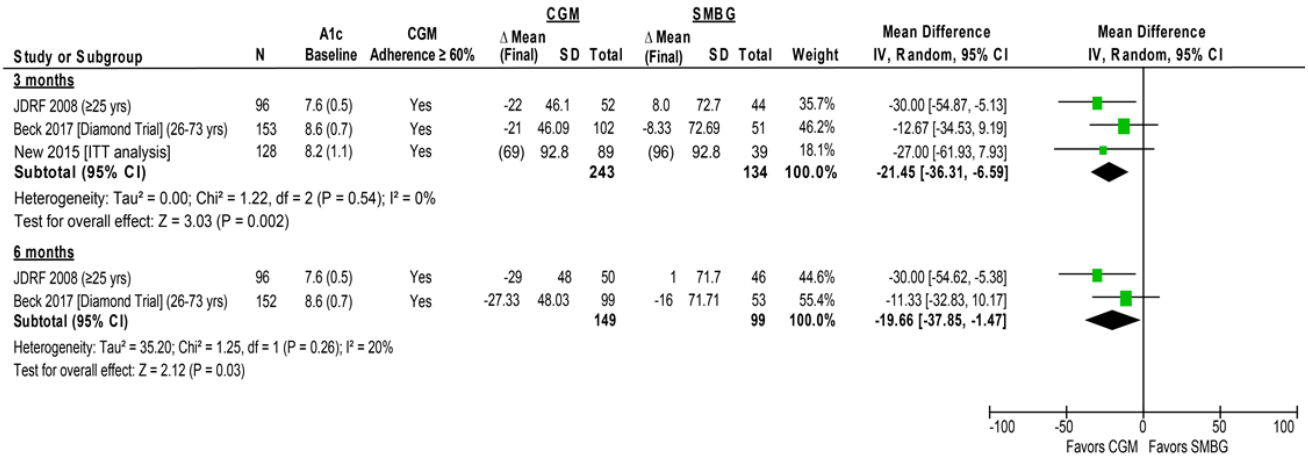
Hypoglycemia (<70 mg/dL)

Randomized controlled trials

One parallel trial found no difference between CGM and SMBG for the number of hypoglycemic events standardized per day at 6 months (MD 0.1, 95% CI-0.2 to 0.5, p=0.40) at a threshold of <72 mg/dL or in the percent of time during monitoring spent in a hypoglycemic range (MD 0.2, 95% CI-1.4 to 1.9).[64] Across three parallel trials,[16,82,113] mean differences in the minutes per day spent at glucose levels <70

mg/dL between groups at 3 months (3 trials, pooled MD -21.45 minutes (95% CI -36.31 to -6.59, I^2=0%) and at 6 months (2 trials pooled MD -19.66 minutes, 95% CI -37.85 to -1.47, I^2=20%) were statistically significant, but clinical significance of the effect size is not clear (Figure 21). Across two cross-over trials, CGM was associated with a decrease in hypoglycemia, as measured by percent of time spent in the hypoglycemic range (<70 mg/dL),[91,152] Table 23. In both trials, the percent of time spent in this range was less in patients using CGM compared to SMBG (both p<0.0001). The clinical significance of the effect sizes is unclear.

Figure 21. CMG vs. SMBG in parallel RCTs in adults: Minutes per day in the hypoglycemia range (<70mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years.

Two other trials report no difference between CGM and SMBG regarding area above[16] or area under the curve[19] for hypoglycemia at a threshold of 70 mg/dL (Table 23).

The trial of FCGM (moderately high risk of bias) in persons with good glycemic control,[23] reported that CGM was associated with statistically significant reductions in the hours per day spent in the <70mg/dL range, AUC and number of events for this range at both 3 and 6 months (Table 23). Adjusted mean differences (±SD) reported by investigators at 3 and 6 months respectively for hours/day were -1.09 (0.18), and -1.24 (0.24), for number of events were -0.35 (0.09) and -0.45 (0.09) and for AUC -25.14 (5.32) and -0.45 (0.09); p-values for all outcomes were <0.0001.

Table 23. Hypoglycemia in adults with T1DM from parallel trials and cross-over trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n) or median (IQR) (n)	SMBG Mean ± SD (n) or median (IQR) (n)	MD (95% CI) or MD (SE)	p-value
Traditional CGM parallel trials						
Hermanides 2011 *Moderately Low*	# of hypoglycemic events (standardized per day)	Baseline	0.7 ± 0.1 (n=40)	0.5 ± 0.5 (n=31)	0.2 (NR)	NR
		6 mos	0.7 ± 0.7 (n=40)	0.6 ± 0.7 (n=31)	0.1 (-0.2 to 0.5)	0.40
	% of total monitoring time in hypoglycemia (minutes <72 mg/dl)	Baseline	3.9 ± 4.7 (n=40)	2.5 ± 2.8 (n=31)	1.4 (NR)	NR
		6 mos	2.7 ± 3.4 (n=40)	2.5 ± 3.6 (n=31)	0.2 (-1.4 to 1.9)	0.79
DIAMOND trial Beck 2017 *Moderately Low*	AAC* Hypoglycemia (70 mg/dL)	Baseline	0.5 (0.3 to 01.1) (n=105)	0.7 (0.2 to 01.4) (n=53)	NR	NR
		3 mos	0.4 (0.1 to 0.6) (n=102)	0.4 (0.2 to 1.5) (n=51)	NR	NR
		6 mos	0.3 (0.1 to 0.5) (n=99)	0.6 (0.1 to 1.1) (n=53)	NR	NR
STAR 3 trial Bergenstal 2010 *Moderately Low*	AUC Hypoglycemia (<70 mg/dL)	Baseline	0.28 ± 0.54 (n=169)	0.31 ± 0.49 (n=167)	NR	NR
		12 mos	0.25 ± 0.44 (n=169)	0.29 ± 0.55 (n=167)	NR	NR
	AUC Hypoglycemia (<50mg/dL)	Baseline	0.02 ± 0.10 (n=169)	0.02 ± 0.07 (n=167)	NR	NR
		12 months	0.02 ± 0.04 (n=169)	0.03 ± 0.09 (n=167)	NR	0.160
Flash glucose monitoring parallel trials						
Bolinder 2016 *Moderately High*	Hypoglycemia <70 mg/dL hours/day	Baseline	3.38 ± 2.31 (n=119)	3.44 ± 2.62 (n=120)	NR	NR
		3 mos	1.91 ± 1.42 (n=119)	3.03 ± 2.21 (n=120)	Adj MD -1.09 (0.18)	<0.0001
		6 mos	2.03 ± 1.93 (n=119)	3.27 ± 2.58 (n=120)	Adj MD -1.24 (0.24)	<0.0001
	Hypoglycemic events <70 mg/dL	Baseline	1.81 ± 0.90 (n=119)	1.67 ± 0.80 (n=120)	NR	NR
		3 mos	1.30 ± 0.77 (n=119)	1.59 ± 0.83 (n=120)	Adj MD -0.35 (0.09)	<0.0001
		6 mos	1.32 ± 0.81 (n=119)	1.69 ± 0.83 (n=120)	-0.45 (0.09)	<0.0001
	AUC Hypoglycemia (<70 mg/dL, hours/day)	Baseline	53.42 ± 43.56 (n=119)	58.34 ± 57.22 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	28.58 ± 31.15 (n=119)	54.67 ± 60.08 (n=120)	Adj MD -25.14 (5.32)	<0.0001

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n) or median (IQR) (n)	SMBG Mean ± SD (n) or median (IQR) (n)	MD (95% CI) or MD (SE)	p-value
	Hypoglycemia <55 mg/dL hours/day	Baseline	1.59 ± 1.42 (n=119)	1.77 ± 1.86 (n=120)	NR	NR
		3 mos	0.74 ± 0.75 (n=119)	1.48 ± 1.57 (n=120)	Adj MD -0.68 (0.13)	<0.0001
		6 mos	0.80 ± 0.96 (n=119)	1.65 ± 1.97 (n=120)	Adj MD -0.82 (0.175)	<0.0001
	Hypoglycemic events <55 mg/dL	Baseline	0.96 ± 0.65 (n=119)	0.92 ± 0.73 (n=120)	NR	NR
		3 mos	0.51 ± 0.42 (n=119)	0.82 ± 0.67 (n=120)	Adj MD -0.33 (0.06)	<0.0001
		6 mos	0.56 ± 0.55 (n=119)	0.92 ± 0.74 (n=120)	Adj MD -0.38 (0.074)	<0.0001
	AUC Hypoglycemia (<55 mg/dL, hours/day)	Baseline	16.04 ± 17.46 (n=119)	18.94 ± 23.22 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	7.59 ± 10.25 (n=119)	17.69 ± 26.34 (n=120)	Adj MD -9.67 (2.29)	<0.0001
	Hypoglycemia <45 mg/dL hours/day	Baseline	0.85 ± 1.03 (n=119)	1.04 ± 1.36 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	0.38 ± 0.58 (n=119)	0.96 ± 1.57 (n=120)	Adj MD -0.55 (0.14)	<0.0001
	Hypoglycemic events <45 mg/dL	Baseline	0.56 ± 0.52 (n=119)	0.59 ± 0.60 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	0.29 ± 0.36 (n=119)	0.56 ± 0.59 (n=120)	Adj MD -0.26 (0.06)	<0.0001
	AUC Hypoglycemia (<45 mg/dL, hours/day)	Baseline	3.99 ± 5.36 (n=119)	5.00 ± 7.10 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	1.74 ± 2.91 (n=119)	4.73 ± 8.66 (n=120)	Adj MD -2.88 (0.75)	0.0002
	Hypoglycemia <40 mg/dL hours/day	Baseline	0.59 ± 0.85 (n=119)	0.75 ± 1.11 (n=120)	NR	NR
		3 mos	0.23 ± 0.34 (n=119)	0.60 ± 1.02 (n=120)	Adj MD -0.33 (0.09)	0.0003
		6 mos	0.26 ± 0.47 (n=119)	0.73 ± 1.41 (n=120)	Adj MD -0.46 (0.12)	0.0003
	Hypoglycemic events <40 mg/dL	Baseline	0.39 ± 0.43 (n=119)	0.44 ± 0.51 (n=120)	NR	NR
		3 mos	0.17 ± 0.23 (n=119)	0.36 ± 0.50 (n=120)	Adj MD -0.18 (0.05)	<0.0001

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n) or median (IQR) (n)	SMBG Mean ± SD (n) or median (IQR) (n)	MD (95% CI) or MD (SE)	p-value
		6 mos	0.19 ± 0.29 (n=119)	0.43 ± 0.55 (n=120)	Adj MD -0.22 (0.05)	<0.0001
	Severe hypoglycemic events‡	6 mos	2/120 (2%) (2 events)	3/121 (2%) (4 events)	0.67 (0.11 to 3.95)§	0.66
Crossover trials						
GOLD trial Lind 2017 Treatment period: 26 wks Washout: 17 wks *Moderately High*	% of time spent in hypoglycemic range (<70 mg/dL)	Baseline	5.52% ± 4.33% (n=69)	5.12% ± 4.24% (n=73)	NR	NR
		Across both treatment periods**	2.79% ± 2.97% (n=69)	4.79% ± 4.03% (n=73)	-2.0 (-2.83 to -1.17)§	<0.0001
IN CONTROL van Beers 2016 Treatment period: 16 wks Washout: 12 wks *Moderately High*	Time spent in hypoglycemic range; hours/day (<70 mg/dL) CGM-derived events per week	Baseline	NR	NR	NR	NR
		Across both treatment periods†† (end of both 16 week intervention periods),	1.6 (1.3 to 2.0) Events/wk 10.1 (8.7 to 11.4) (n=26)	2.7 (2.4 to 3.1) Events/wk 11.1 (9.8 to 12.5) (n=26)	-1.1 (-1.4 to-0.8) Events/wk MD -1.1 (01.4 to -0.8)	<0.0001 for both
	AUC ≤3.9 mmol/l per 24 hours (mmol/l per minute)‡‡	Across both treatment periods†† (end of both 16 week intervention periods)	62.9 (45.1, to 80.7) (n=26)	115.8 (97.8 to 133.8) (n=26)	-52.9 (-97.8 to -37.7)	<0.0001

AUC: area under curve; AAC: area above curve; CGM: Continuous Glucose Monitoring; CI: confidence interval; F/U: follow-up; HbA1C: hemoglobin A1C; mos: months; NR: not reported; SD: standard deviation; SE: standard error; SMBG: self-monitoring of blood glucose; wk: week

*Number of events, standardized per day. An event was counted when the sensor glucose value crossed the hyper- or hypoglycaemia threshold, followed by a 30-min period between 4.0 and 11.1 mmol／l

†Measure reported throughout the study as "area above the curve" along with the following footnote: "area above (the glucose) curve 70mg/dL reflects both percentage and severity of glucose values in the hypoglycemic range."

‡One severe hypoglycemic event occurred during the baseline run-in phase. In methods section, authors define a severe hypoglycemic event as those requiring third party assistance but the data provided does not explicity link the definition with the events reported.

§Calculated by AAI

** Regression model. Least-square means (95% CIs) and *P* value were calculated with sequence, patient (sequence), treatment period, and treatment as class variables (calculated only for normally distributed variables).

†† Mean difference between combined results of both arms at end of 16-week intervention phase

‡‡3.9 mmol/l converts to 70.2 mg/dL

Observational studies

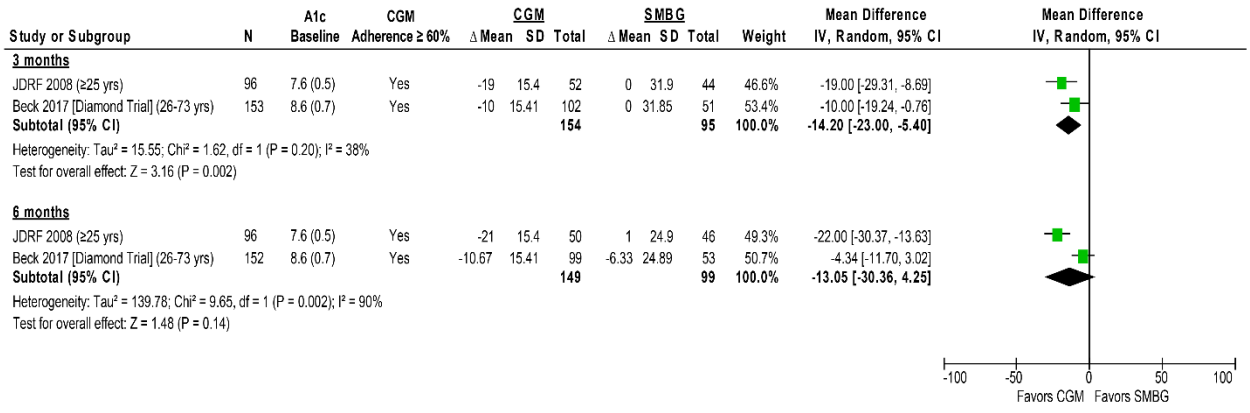
One prospective cohort study[145] compared 27 CGM users (DexCom G4 and Enlite sensor devices) with 18 SMBG patients over the course of 12 months. Mean patient age was 36 ± 13 years and mean baseline HbA1c% was 8.3% ± 0.9%. A significant reduction from baseline to 12 months in time spent in hypoglycemia (range <70 mg/dl) was observed in the CGM group (8% ± 4% vs. 6% ± 3%; p<0.01); no significant change was seen in those performing SMBG (6% ± 4% vs. 7% ± 5%; p=0.68). The authors do not provide an effect estimate for the difference in change between groups.

A second observational study reported on hypoglycemia, but provided data for the CGM arm only. The study was a follow-up study of the JDRF 2008 trial [80] which evaluated adults (n = 74, age ≥25) who had been randomized initially to SMBG and who were subsequently offered CGM at the end of the trial for up to 26 weeks. A statistically significant reduction from baseline (i.e., the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group) to 6 months was seen in minutes per day spent in hypoglycemic range ≤70 mg d/l (mean 55 vs. 45, respectively, p=0.02) and ≤60 mg/dl (mean 19 vs. 11, respectively, p=0.006) in adults using CGM.

Hypoglycemic range ≤55 mg/dL

Although there was a small decrease favoring CGM over SMBG in the mean minutes per day in the hypoglycemia range <55 mg/dL across two trials[16,82] at 3 months (pooled MD -14.2 minutes/day), Figure 22, there were no differences between groups at 6 months (pooled MD -13.1 minutes/day); the clinical significance of these effect estimates is unclear. One parallel trial reported no difference between CGM (mean 0.02 ± 0.04) and SMBG (mean 0.03 ± 0.09) with regard to area under the curve (AUC) at a threshold of <50mg/dL through 12 months (Table 23).[19]

Figure 22. CMG vs. SMBG in parallel RCTs in adults; Minutes per day in the hypoglycemia range (<55 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years.

FCGM was associated with less time at glucose levels <55 mg/dL at both 3 months (adjusted MD -0.68 ± 0.13 hours/day) and 6 months (adjusted MD -0.82 ± 0.175 hours/day) and fewer events at this threshold

(3 month adjusted MD -0.33 ± 0.06, 6 month adjusted MD -0.38 ± 0.74) in one trial[23]: p-values for all results were <0.001. Authors also report a significant difference favoring FCGM for AUC at this threshold (Table 23).

Adherence in observational studies

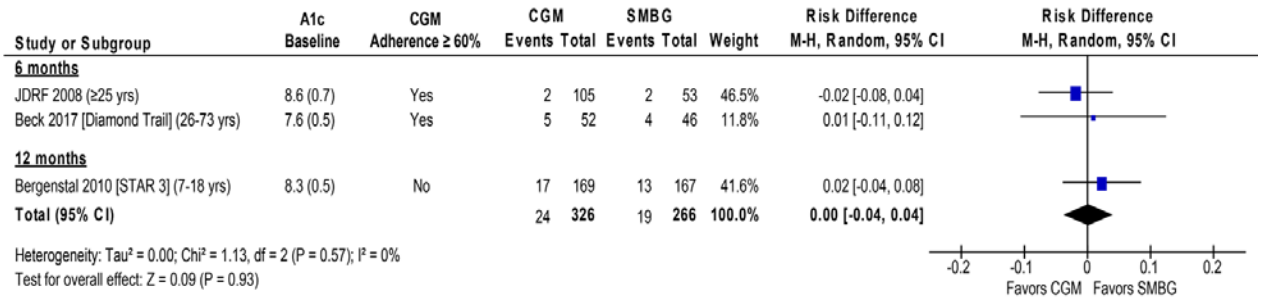
One prospective registry study (n=1479, age ≥18 years), [93] using data from the DPV diabetes documentation and quality management system in Germany and Austria, found no statistically significant difference in the rate of hypoglycemia (not otherwise specified) when comparing those who used CGM at least 30 days versus less than 30 days or no use (data not provided).

Severe Hypoglycemic Events

Randomized controlled trials

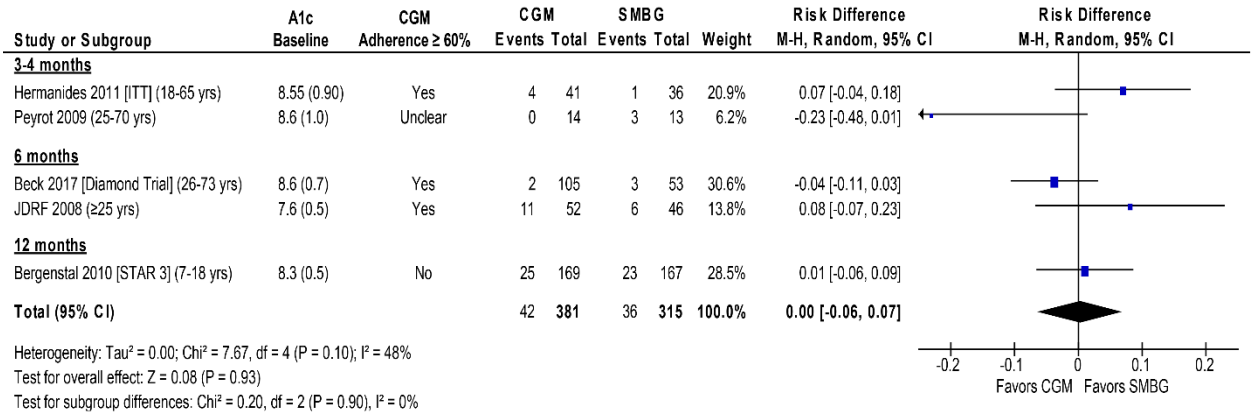
Across parallel RCTs, there were no apparent differences between CGM or SMBG at across time points up to 12 months in the proportion of adults experiencing ≥ 1 severe hypoglycemic events (3 trials, pooled RD 0%, 95% CI -4% to 4%, I^2=0%),[16,19,82] (Figure 23) or in the number of severe hypoglycemic events (4 trials, pooled RD 0%, 95% CI-6% to 7%, I^2=46%).[16,64,82,121] (Figure 24). It is likely that studies may have been underpowered to detect differences between treatments for these rare events.

Figure 23. CMG vs. SMBG in parallel RCTs in adults: Proportion of patients with ≥ 1 severe hypoglycemic events



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years.

Figure 24. CMG vs. SMBG in parallel RCTs in adults: Number of severe hypoglycemic events*



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

*Peyrot was at moderately high risk of bias and did not provide a definition of severe hypoglycemic event; Severe was defined for other trials as events requiring third party assistance or need for resuscitative actions or loss of consciousness or seizure.

Across four crossover trials, results were somewhat mixed. There were no differences in numbers of events in two trials [91,150] or in mean number of events per 4 weeks [89] in a third trial. The largest trial (N = 161)[91] reported 1 event (0.04 per 1000 patient-years) versus 5 events (0.19 per 1000 patient-years), p =0.7545. By contrast one small trial (n = 52) reported, fewer total events during CGM phases than during SMBG phases (14 vs. 34 events, p = 0.033) and fewer adults with ≥1 severe hypoglycemic events (19% versus 35%), however these later results were no longer statistically significant when adjusted for study duration (adjusted OR 0.48, 95% CI0.2 to 1.0, p=0.062), Table 24. Definitions of severe events are provided in the table and were consistent with definitions provided for the parallel trials. Studies were likely underpowered to detect differences between groups.

The trial of FCGM[23] reported that 2% (n =2) of participants in the FCGM and 2% (n=3) in the SMBG group experienced hypoglycemic severe adverse events and that the number of events was 2 and 4 in the respective groups (Table 24). One event occurred during the baseline phase but authors do not indicate in which group it occurred. While in the methods the authors indicate that they assessed the number of severe events, defined as those requiring third party assistance, it is not clear that the events reported were linked to that definition. The study was likely underpowered to detect differences between groups.

Table 24. Severe hypoglycemia in adults with T1DM from parallel RCTs and cross-over trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n) or % (n/N)	SMBG Mean ± SD (n) or % (n/N)	RR (95% CI)	p-value
Traditional CGM parallel trials						
Bergenstal 2010 STAR 3 *Moderately Low*	AUC Severe Hypoglycemia (<50mg/dL)	Baseline	0.02 ± 0.10 (n=169)	0.02 ± 0.07 (n=167)	NR	NR
		12 months	0.02 ± 0.04 (n=169)	0.03 ± 0.09 (n=167)	NR	0.160
Flash glucose monitoring parallel trials						
Bolinder 2016 *Moderately High*	Number of severe hypoglycemic events	6 months	2% (2/119) (n events NR)	3% (3/120) (n events NR)	0.67 (0.11 to 3.95)*	0.65*

Author year ; treatment period length *ROB*	Outcome	Timing	CGM Periods Mean ± SD or # events (per patient years) or % (n/N) (n events)	SMBG Periods Mean ± SD or # events (per patient years) or % (n/N)(n events)	MD (95% CI) or OR (95% CI)	p-value
Crossover trials						
GOLD trial Lind 2017 Treatment periods: 26 weeks; Washout 17 weeks **N=161** *Moderately High*	Episodes of acute/severe hypoglycemia Unconsciousness from hypoglycemia or requiring assistance from another person)	Baseline	1.90 ± 1.48/wk 0.101 ± 0.425/ last yr	2.36 ± 2.23/wk 0.042 ± 0.262/ last yr	NR	NR
		During washout period	7 events (0.41 per 1000 patient-years)		NR	NR
		Across both treatment periods†	1 event (0.04 per 1000 patient-years)	5 events (0.19 per 1000 patient-years)	NR	0.7545†
IN CONTROL van Beers 2016 Treatment periods: 16 weeks; Washout: 12 weeks **N= 52** *Moderately High*	Episodes of severe hypoglycemia	Baseline (hypoglycemia questionnaire)	>1 episode per week: 4% (2/46) >1 episode per month: 15% (7/46)		NR	NR
		Across both treatment periods	n/N NR (14 events)	n/N NR (34 events)	NR	0.033†
	Patients with ≥1 severe hypoglycemic event	Across both treatment periods‡	19% (10/52) (14 events§)	35% (18/52) (34 events**)	OR 0.45 (0.23 to 0.87) Adj. OR 0.48 (0.22 to 1.04)	Un-Adj.: 0.018 Adj.: 0.062
Langeland 2012	Episodes of acute/severe hypoglycemia	Baseline	NR	NR	NR	NR
		Across both treatment periods	8.2 ± 1.6 per 4 weeks	7.3 ± 1.4 per 4 weeks	0.90 (-0.18 to 1.98) per 4 weeks	0.67

Author year ; treatment period length *ROB*	Outcome	Timing	CGM Periods Mean ± SD or # events (per patient years) or % (n/N) (n events)	SMBG Periods Mean ± SD or # events (per patient years) or % (n/N)(n events)	MD (95% CI) or OR (95% CI)	p-value
Treatment period: 4 wks Washout: 8 wks **N= 30** *Moderately High*	(Need of help from others)					
Tumminia 2015 Treatment period: 6 mos Washout: 2 mos **N= 20** *Moderately High*	Episodes of acute/severe hypoglycemia (<50 mg/dL) (requiring support of another person)	Across both treatment periods (for all participants)	0% (0/10) (0 events)	0% (0/10) (0 events)	0	NR

CGM: Continuous Glucose Monitoring; CI: confidence interval; F/U: follow-up; HbA1C: hemoglobin A1C; NR: not reported; SMBG: self-monitoring of blood glucose; SD: standard deviation
*Calculated by AAI
†Regression model. Least-square means (95% CIs) and *P* value were calculated with sequence, patient (sequence), treatment period, and treatment as class variables (calculated only for normally distributed variables).
‡Result of the related-samples Wilcoxon signed-rank test done on rates of 16-week severe hypoglycaemic events (requiring third-party assistance) per 100 patient-months (p=0.033)
§4 seizure/coma, 1 hospitalization, 9 required third-party assistance
**4 seizure/coma, 1 hospitalization, 29 required third-party assistance

Observational studies

Three observational studies, one prospective cohort study, [145] one retrospective registry,[158] and one single-arm extension study of the JDRF 2008 trial,[80] reported episodes of severe hypoglycemia.

The prospective cohort study[145] compared 27 CGM users (DexCom G4 and Enlite sensor devices) with 18 SMBG patients over the course of 12 months. Mean patient age was 36 ± 13 years and mean baseline HbA1c% was 8.3% ± 0.9%. No episodes of severe hypoglycemia, defined as an event requiring assistance from another person or neurological recovery in response to restoration of plasma glucose to normal, were reported in the CGM group compared with one (6%) in the SMBG group; the difference between groups was not statistically significant (p=0.221) and this study was likely underpowered to detect such rare events.

One retrospective registry study reported episodes of severe hypoglycemia, defined as drops in blood glucose resulting in seizure or loss of consciousness, among adults with T1DM. [158] The frequency of one or more severe hypoglycemic events through 3 months was not significantly different between the CGM and SMBG groups among those age 18 to less than 26 years (10% vs. 8%, respectively; adjusted OR 1.7,

95% CI 0.8 to 3.4, p=0.16) and age 26 years or older (11% vs. 11%; adjusted OR 1.3, 95% CI 1.0 to 1.7, p=0.04).

One observational study[80] of the JDRF 2008 trial reported on severe hypoglycemia, but provided only data for the CGM group. This study evaluated adults (n=78, age ≥25 years) who had been randomized initially to SMBG and who were subsequently offered CGM at the end of the trial for up to 26 weeks. During the 6 months post-RCT, eight (10%) adults experienced a severe hypoglycemic event defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions. There were a total of nine events, two of which resulted in seizure or loss of consciousness. The incidence rate was 23.0 per 100 person-years, which tended to be lower than the incidence rate during the previous 6-month control period of the RCT (33.7 per 100 person-years). Similarly, significant improvement from baseline (i.e., the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group) to 6 months was reported with regard to fewer minutes per day spent in a hypoglycemic range of ≤50 mg d/l (mean 5 vs. 4, respectively, p=0.02) in adults using CGM. The clinical significance of this difference is unclear.

Adherence in observational studies

One retrospective database study also evaluated the effect of frequency and consistency of CGM use on hypoglycemic episodes in adults with type 1 diabetes[158] with no association found between the two variables. In subjects age 18 to less than 26 years who used the device 6 or more, 4 to 6, and less than 4 days per week, the frequency of hypoglycemic events over 3 months was 9.8%, 5.9% and 1.9%, respectively (p=0.12); the ORs for the comparison of 6 or more days and 4 to 6 days versus less than 4 days of CGM use were 5.5 (95% CI 0.6, 49.2) and 3.2 (95% CI 0.3 to 36.6), respectively. Corresponding values in adults age 26 years or older were 12.2%, 10.1% and 9.1%; ORs 1.4 (95% CI 0.8 to 2.3) and 1.1 (95% CI 0.6 to 2.3).

Nocturnal Hypoglycemia (<70 mg/dL, < 50 mg/dL)

Randomized controlled trial

Nocturnal hypoglycemia was reported in one parallel trial[16] and one cross-over trial, [152] (Table 25). At 6 months in the parallel trial, the median percent of time spent at night in the hypoglycemic ranges <70 mg/dL and area under the curve were significantly lower in the CGM group compared with the SMBG group (effect estimates not reported, p = 0.003 and 0.0002 respectively) as were median percent of time spent at <60 mg/dL and <50 mg/dL (p = 0.002 and 0.001 respectively).[16] Similarly across the two 16-week treatment periods in the cross-over trial, the percent of time spent at night in the <70 mg/dL range was significantly lower (MD 5.7, 95% CI
-8.2 to -3.2, p =<0.0001) during the CMG phases compared with the SMBG phases as were the number of CGM-derived events per night (MD -0.07, 95% CI-0.11 to -0.02, p=0.003).[152] It is not clear whether these differences are clinically important.

Data for nocturnal hypoglycemia at a threshold of <50mg/dL are limited and were reported only in the parallel trial[16]: the median percent of time spent in this range at 6 months was significantly lower in the

CGM group versus the SMBG group (medians 0% vs. 0.3%, p=0.001, effect sizes not reported). It is not clear whether this difference is clinically important.

In one trial FCGM[23] was associated with less time (hours/day) in the hypoglycemic range thresholds of <70 mg/dL, < 55 mg/dL, and <45 mg/dL and fewer events at below each of these thresholds at night (Table 25). In addition AUC was smaller and thus favored FCGM at each of these thresholds.

Table 25. Nocturnal hypoglycemia in adults with T1DM from parallel RCTs and cross-over trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM Median (IQR) (n)	SMBG Median (IQR) (n)	MD (95% CI) or MD (SE)	p-value
Traditional CGM parallel trials						
DIAMOND trial Beck 2017 *Moderately High*	% time <70 mg/dL	Baseline	5.5% (2.2%-9.6%) (n=105)	7.2% (2.3%-11.0%) (n=53)	NR	NR
		3 mos	3.1% (0.6%-7.6%) (n=102)	7.6% (0%-12.8%) (n=51)	NR	NR
		6 mos	1.8% (0.1%-4.9%) (n=99)	5.2% (0.9%-9.4%) (n=53)	NR	0.003*
	% time <60 mg/dL,	Baseline	2.9 (1.0%-5.8%) (n=105)	4.0% (1.7%-8.5%) (n=53)	NR	NR
		3 mos	1.3% (0%-3.1%) (n=102)	3.0% (0%-8.9%) (n=51)	NR	NR
		6 mos	0.6% (0%-2.3%) (n=99)	2.4% (0%-6.3%) (n=53)	NR	0.002*
	% time <50 mg/dL,	Baseline	1.1% (0.3%-3.0%) (n=105)	1.8% (0.2%-4.7%) (n=53)	NR	NR
		3 mos	0% (0%-1.1%) (n=102)	0.8% (0%-5.1%) (n=51)	NR	NR
		6 mos	0% (0%-0.9%) (n=99)	0.3% (0%-2.4%) (n=53)	NR	0.001*
	AUC <70 mg/dL,	Baseline	0.7 (0.2-1.5) (n=105)	1.0 (0.4-2.1) (n=5 3)	NR	NR
		3 mos	0.3 (0-0.8) (n=102)	0.7 (0-2.2) (n=51)	NR	NR
		6 mos	0.2 (0-0.6) (n=99)	0.5 (0-1.5) (n=53)	NR	0.002*
Flash glucose monitoring parallel trials						
Bolinder 2016 *Moderately high*	Nocturnal hypoglycemia <70 mg/dL hours/day	Baseline	1.32 ± 1.07 (n=119)	1.48 ± 1.29 (n=120)	NR	NR
		3 mos	0.72 ± 0.70 (n=119)	1.26 ± 0.99 (n=120)	Adj MD -0.48 (0.10)	<0.0001
		6 mos	0.68 ± 0.97 (n=119)	1.23 ± 1.10 (n=120)	Adj MD -0.47 (0.12)	<0.0001
	Nocturnal hypoglycemic	Baseline	0.47 ± 0.32 (n=119)	0.46 ± 0.29 (n=120)	NR	NR

Author year *ROB*	Outcome	Timing	CGM Median (IQR) (n)	SMBG Median (IQR) (n)	MD (95% CI) or MD (SE)	p-value
	events <70 mg/dL	3 mos	0.31 ± 0.28 (n=119)	0.42 ± 0.28 (n=120)	Adj MD -0.11 (0.03)	0.0010
		6 mos	0.27 ± 0.23 (n=119)	0.40 ± 0.29 (n=120)	Adj MD -0.14 (0.03)	<0.0001
	Nocturnal hypoglycemia <55 mg/dL hours/day	Baseline	0.62 ± 0.60 (n=119)	0.75 ± 0.83 (n=120)	NR	NR
		3 mos	NR	NR (n=120)	NR	NR
		6 mos	0.31 ± 0.43 (n=119)	0.66 ± 0.08 (n=120)	Adj MD -0.32 (0.07)	<0.0001
	Nocturnal hypoglycemic events <55 mg/dL	Baseline	0.34 ± 0.27 (n=119)	0.36 ± 0.34 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	0.19 ± 0.24 (n=119)	0.30 ± 0.28 (n=120)	Adj MD -0.11 (0.03)	0.0005
	Nocturnal hypoglycemia <45 mg/dL hours/day	Baseline	0.36 ± 0.44 (n=119)	0.48 ± 0.66 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	0.15 ± 0.25 (n=119)	0.43 ± 0.65 (n=120)	Adj MD -0.25 (0.06)	<0.0001
	Nocturnal hypoglycemic events <45 mg/dL	Baseline	0.23 ± 0.23 (n=119)	0.27 ± 0.31 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	0.11 ± 0.16 (n=119)	0.21 ± 0.22 (n=120)	Adj MD -0.09 (0.02)	<0.0001
Author year ; treatment period length (ROB)	**Outcome**	**Timing**	**CGM Periods Mean (95% CI)**	**SMBG Periods Mean (95% CI)**	**MD (95% CI)**	**p-value**
Crossover trials						
IN CONTROL van Beers 2016 Treatment period: 16 wks Washout: 12 wks **N=52** *Moderately High*	Hypoglycemia <70 mg/dL	Baseline	NR	NR	NR	NR
		Across both treatment periods†	% of time: 7.6 (5.3 to 9.8) CGM-derived events per night: 0.26 (0.21 to 0.31)	% of time: 13.3 (11.0 to 15.5) CGM-derived events per night: 0.33 (0.28 to 0.38)	% of time: -5.7 (-8.2 to –3.2) CGM-derived events per night: -0.07 (-0.11 to -0.02)	% of time: <0.0001 CGM-derived events per night: 0.003

CGM: Continuous Glucose Monitoring; CI: confidence interval; F/U: follow-up; HbA1C: hemoglobin A1C; NR: not reported; SD: standard deviation; SE: standard error; SMBG: self-monitoring of blood glucose;

*Treatment group comparisons made using analysis of covariance models, adjusted for the corresponding baseline value, baseline HbA1c and clinical site as a random effect using pooled data from 12 and 24 weeks.

†Outcomes are percentage of time spent with glucose concentration ≤3·9 mmol/L (70mg/dL)

Observational studies

One observational study reported on nocturnal hypoglycemia in adults with type 1DM, however only noncomparative data was available. The study was a subanalysis of the JDRF 2008 trial[80] which evaluated adults (n=74, age ≥25 years) who had been randomized initially to SMBG who were offered CGM at the end of the trial for up to 26 weeks. No significant improvement from baseline (i.e., the time of initiation of CGM use after the 6 months in the JDRF RCT SMBG group) to 6 months was reported in minutes per night spent in hypoglycemic range ≤70 mg d/l (mean 12 vs. 11, respectively) or ≤50 mg d/l (mean 0 vs. 1, respectively) in adults using CGM (p-values not reported).

Secondary Intermediate Outcomes

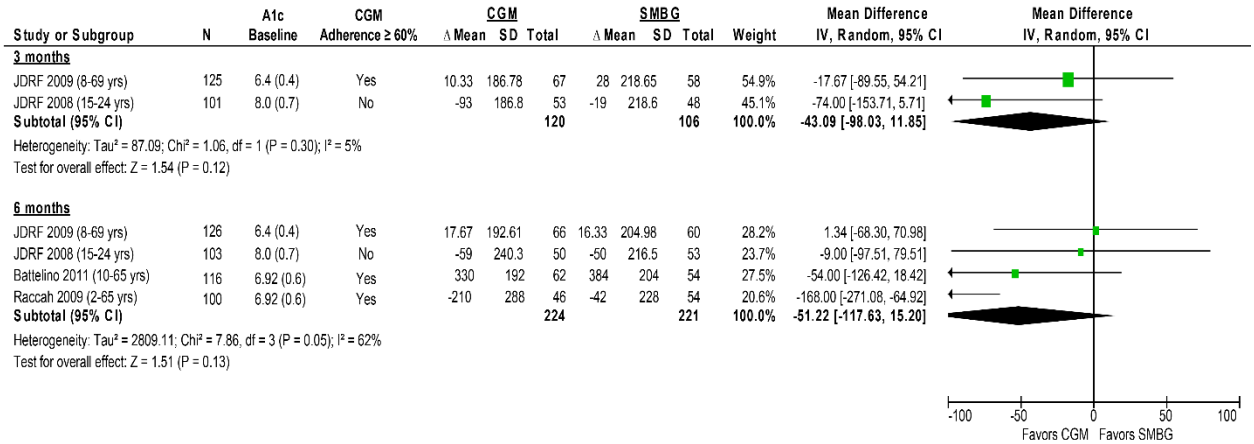
Hyperglycemia

Randomized controlled trials

Across two parallel trials, instability of effect size estimate preclude drawing firm conclusions.

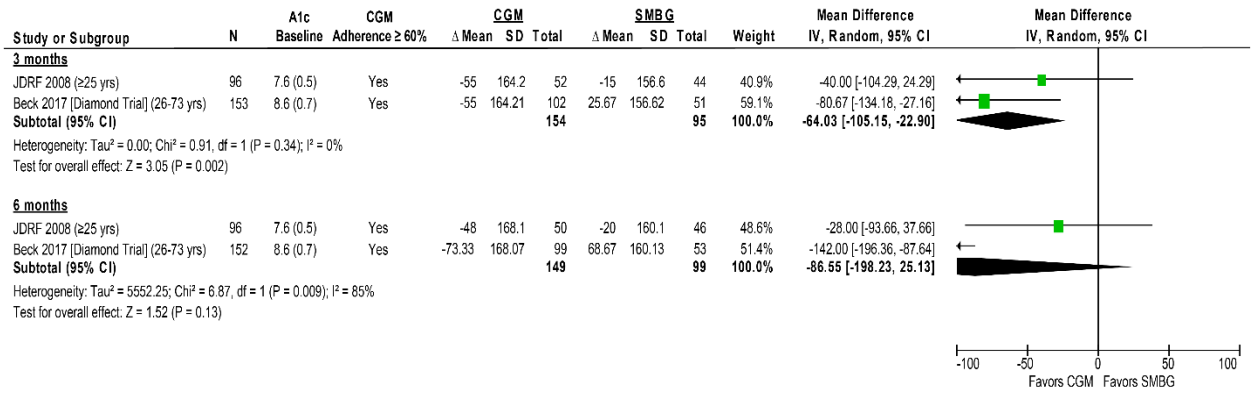
There was no clear difference between CGM and SMBG in adults with regard to minutes spent in a hyperglycemic range (>180 mg/dL) across two trials [16,82] at 3 months (Figure 25). The pooled estimate at 6 months suggests less time in this range with CGM vs SMBG. The wide confidence intervals at both time frames suggest substantial variability and instability in estimated effect size. Across the same two trials, for minutes per day spent in a hyperglycemic range >250, at 3 months, data suggests less time in this range with CGM vs. SMBG and no difference between groups at 6 months (Figure 26). Again, wide confidence intervals at both time frames suggest substantial variability and instability in estimated effect size.

Figure 25. CMG vs. SMBG in parallel RCTs in adults: Minute per day in hyperglycemic range (>180 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 26. CMG vs. SMBG in parallel RCTs in adults: Minute per day in hyperglycemic range (>250 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Across two cross-over trials[150,152] reporting hyperglycemia, CGM was associated with less time spent in the hyperglycemic range compared to SMBG. In the larger trial, [152] patients spent an average of 5.0 percent less time in the hyperglycemic range during the CGM period compared to the SMBG period (95% CI -6.9% to -3.1%, p <0.0001). In the smaller trial, [150] hyperglycemia was measured as AUC >200. While the mean difference failed to reach statistical significance, likely due to small sample size, AUC>200 was an average of 3.76 mg/dL/day less during the CGM phase compared to the SMBG phase (95% CI -12.06 to 4.54, p = 0.3602).

There was no difference between FCGM and SMBG with regard to the time/day FCGM in hyperglycemic range of >180 mg/dL at 6 months in one trial however the same authors report FCGM was associated with less time spent >240 mg/dL at both 3 and 6 months compared with SMBG.[23] There was no difference between groups at a threshold of >300mg/dL (Table 26).

Table 26. Outcomes measuring hyperglycemia in adults with T1DM from cross-over trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n) or Median (IQR) (n)	SMBG Mean ± SD (n) or Median (IQR) (n)	MD (95% CI) or MD (SE)	p-value
Traditional CGM parallel trials						
Bergenstal 2010 STAR 3 *Moderately low*	AUC Hyperglycemia (>250 mg/dL)	Baseline	8.16±8.31 (n=169)	7.98±7.98 (n=167)	NR	NR
		12 mos	3.74±5.01 (n=169)	7.38±8.62 (n=167)	NR	NR
	AUC Hyperglycemia (>180 mg/dL)	Baseline	28.92±17.80 (n=169)	28.04±17.03 (n=167)	NR	NR
		12 mos	16.06±12.84 (n=169)	26.01±19.52 (n=167)	NR	NR

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n) or Median (IQR) (n)	SMBG Mean ± SD (n) or Median (IQR) (n)	MD (95% CI) or MD (SE)	p-value
Beck 2017 DIAMOND trial *Moderately low*	AUC Hyperglycemia (>180 mg/dL)	Baseline	34 (25 to 46) (n=105)	33 (26 to 45) (n=53)	NR	NR
		3 mos	29 (18 to 41) (n=102)	34 (24 to 49) (n=51)	NR	NR
		6 mos	26 (16 to 42) (n=99)	41 (27 to 54) (n=53)	NR	NR
Flash glucose monitoring parallel trials						
Bolinder 2016 *Moderately high*	Hyperglycemia >180 mg/dL hours/day	Baseline	5.62 ± 2.48 (n=119)	5.80 ± 3.11 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	6.16 ± 3.05 (n=119)	6.08 ± 3.20 (n=120)	Adj MD 0.19 (0.329)	0.5623
	Hyperglycemia >240 mg/dL hours/day	Baseline	1.85 ± 1.44 (n=119)	1.91 ± 1.70 (n=120)	NR	NR
		3 mos	1.73 ± 1.41 (n=119)	2.36 ± 2.06 (n=120)	Adj MD -0.60 (0.19)	0.0016
		6 mos	1.67 ± 1.36 (n=119)	2.06 ± 1.61 (n=120)	Adj MD -0.37 (0.16)	0.025
	Hyperglycemia >300 mg/dL hours/day	Baseline	0.48 ± 0.58 (n=119)	0.49 ± 0.69 (n=120)	NR	NR
		3 mos	NR	NR	NR	NR
		6 mos	0.34 ± 0.46 (n=119)	0.44 ± 0.54 (n=120)	Adj MD -0.11 (0.06)	0.0684
Author year ; treatment period length *ROB*	**Outcome**	**Timing**	**CGM Periods Mean ± SD or mean (95% CI) (n)**	**SMBG Periods Mean ± SD or mean (95% CI) (n)**	**MD (95% CI)**	**p-value**
Crossover trials						
IN CONTROL van Beers 2016 Treatment periods: 16 wks; Washout: 12 wks *Moderately High*	% of time spent in hyperglycemic range (>180 mg/dl)*	Baseline	NR	NR	NR	NR
		Across both treatment periods†	28.2% (25.1% to 31.3%) (n = 52)	33.2% (30.0% to 36.3%) (n = 52)	-5.0% (-6.9% to -3.1%)	<0.0001
Tumminia 2015 Treatment periods: 6 mos Washout phase: 2 mos *Moderately High*	AUC > 200 (mg/dL/day) (for participants with >40% CGM usage)	Baseline† (n= 14)	23.17 ± 16.99	19.36 ± 13.16	NR	NR
		End of period† (n = 6)	17.28 ± 12.50	21.04 ± 8.48	-3.76 (-12.06 to 4.54)‡	0.3602

CGM: Continuous Glucose Monitoring; CI: confidence interval; F/U: follow-up; HbA1C: hemoglobin A1C; NR: not reported; SD: standard deviation; SE: standard error; SMBG: self-monitoring of blood glucose;
*Reported as 10 mmol/l in study, converted to 180 mg/dl by AAI
†Mean difference between combined results of both arms at end of 16-week intervention
‡Calculated by AAI

Observational studies

One observational study reported on hyperglycemia for CGM users only. The study was a follow-up of the JDRF 2008 trial[80] which evaluated adults (n=74, age ≥25 years) who had been randomized initially to SMBG and who were offered CGM at the end of the trial for up to 26 weeks. A statistically significant improvement from baseline to 6 months was reported in minutes per day spent in hyperglycemic range >180 mg d/l (mean 439 vs. 390, respectively, p=0.03) and >250mg d/l (mean 114 vs. 72, respectively, p<0.0001) in this population. The clinical significance of these findings is unclear.

Diabetic Ketoacidosis (DKA)

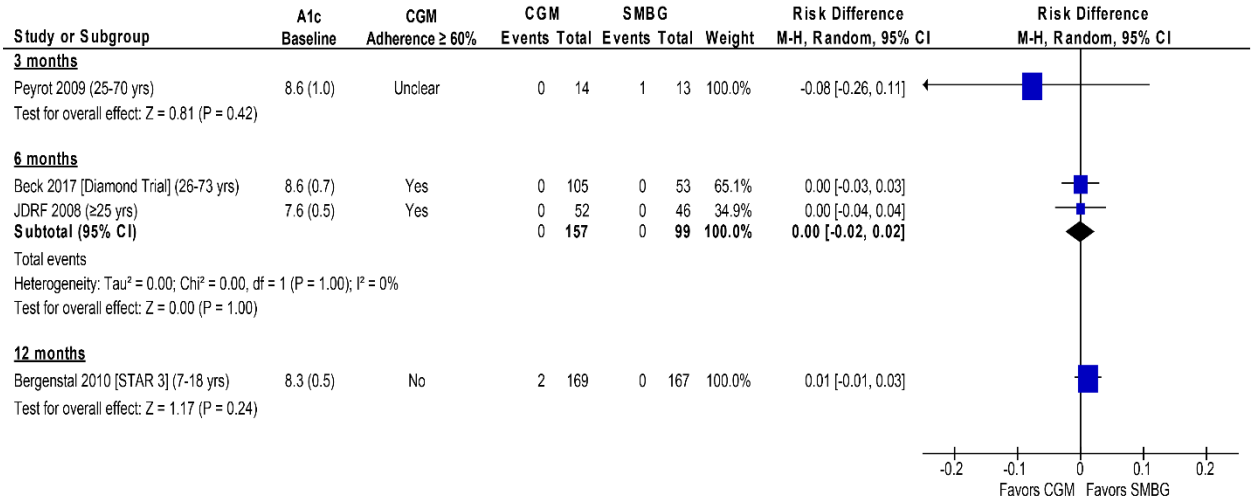
Randomized controlled trials

Parallel arm trials

Four parallel arm trials reported the frequency of DKA. [16,19,82,121] DKA was reported rarely and no differences were seen between the CGM and SMBG groups in any trial at any timepoint (Figure 27). Studies may have been underpowered to detect differences.

DKA was not reported by the trial evaluated FCGM.[23]

Figure 27. CGM vs. SMBG in parallel RCTs in adults: Episodes of DKA



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Cross-over trials

Across two crossover trials reporting DKA, no episodes occurred in either study arm over 4 and 6 months of follow-up. [91,152]

Observational studies

One prospective cohort study[145] compared 27 CGM users (DexCom G4 and Enlite sensor devices) with 18 SMBG patients over the course of 12 months (mean patient age 36 ± 13 years and mean baseline HbA1c 8.3% ± 0.9%) and reported that no episodes of DKA occurred in either group.

One retrospective database study reported episodes of DKA among adults with type 1 diabetes.[158] The frequency of one or more DKA event over 3 months was not significantly different between the CGM and SMBG groups among those age 18 to less than 26 years (4% vs. 8%, respectively; adjusted OR 0.6, 95% CI 0.2 to 1.8, p=0.33) and age 26 years or older (2% vs. 3%; adjusted OR 1.4, 95% CI 0.8 to 2.3, p=0.23). This same study also evaluated the effect of frequency and consistency of CGM use on DKA episodes and found no association between the two variables. In subjects less than age 18 to less than 26 years who used the device 6 or more, 4 to 6, and less than 4 days per week, the frequency of DKA events was 3.9%, 0% and 3.9%, respectively (p=0.38). The adjusted OR for the group using CGM 6 or more days versus less than 4 days per week was 1.9 (95% CI 0.1 to 25.9).

Health-related quality of life

Randomized controlled trials

Results varied across various quality of life measures as reported in four parallel design RCTs in adults with T1DM.[81,113,123,132]; see Appendix I for further details of quality of life. In one trial, there was a slight improvement at 6 months favoring CGM for the Hypoglycemia Fear Survey (HFS) total score and avoidance behavior subscale (but not the worry subscale), as well as for the SF-12 Physical Component Summary (PCS) (but not the SF-12 Mental Component Summary (MCS)), p values range from 0.03 to 0.04[81]; however, there were no significant differences between CGM and SMBG on the Problem Areas in Diabetes (PAID) questionnaire. The second trial reported quality of life at final follow-up (3.3 months) using the Short Form-8 (SF-8) Health Survey questionnaire and the Diabetes Distress Scale.[113] A significant improvement was seen in the CGM with alarms group, but not in the CGM without alarms group, compared with the SMBG group in mean SF-8 Physical Component Summary scores: adjusted mean difference 3.6 (95% CI -0.47 to 6.73), p=0.025, (Appendix Table I). There were no difference between groups for any other measure (SF-8 Mental Component Summary score or Diabetes Distress Scale). In athird trial, diabetes-specific quality of life (HFS worry and avoidant behavior subscale scores) was significantly improved in the CGM group (p<0.001) but no differences were seen between groups regarding generic quality of life measures SF-36 MCS and PCS.[132] This trial also reported satisfaction via the Insulin Delivery System Rating Questionnaire and noted significantly greater improvement in adults who used CGM versus SMBG on measures of Convenience, Efficacy, Overall Preference (p<0.001), and Interference and Well-being (p<0.01) The third trial found that CGM use resulted in a greater increase in hypoglycemic confidence (p=0.01) and a greater decrease in diabetes distress (p=0.01) than SMBG alone; no significant group differences were observed in hypoglycemic worry (HFS) or in the non–diabetes-specific QOL measures evaluated (WHO-5 and EQ-5D-5L).[123]

Two cross-over trials [69,91] reported health-related quality of life and treatment satisfaction (Appendix Table I). Results varied across measures. Both trials used the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and reported statistically significant improvements associated with CGM use compared to SMBG (both p <0.05).The larger trial [91] also evaluated quality of life using the Hypoglycemic Fear Survey (HFS) and the World Health Organization -5 Well Being Index (WHO-5). While CGM was associated with a statistically significant increase in health-related quality of life as measured by the WHO-5 (mean difference 3.54, 95% CI 0.61 to 6.48, p = 0.01), no difference was noted on the HFS (mean difference 0.03, 95% CI -0.05 to 0.10, p=0.45).

The FCGM recipients reported greater treatment satisfaction compared with those in the SMBG group as well as improved perceived frequency of hyperglycemia in one trial.[23] Diabetes quality of life scores, hypoglycemic fear behavior, worry scores and diabetes distress scores were not significantly different between groups (please see details in Appendix I).

Observational studies

A 6-month, single arm extension study of the JDRF 2008 and 2009 trials in subjects ≥18 years (during which the SMBG group received a CGM device and the CGM group continued monitoring for an additional 6 months) reported that adults (n=224) were highly satisfied with CGM use as measured by the Continuous Glucose Monitoring Satisfaction Scale (CGM-SAT).[148] The overall mean score was 3.8 ± 0.5 (out of a 0-5 scale); scores for the "benefit" and "lack of hassle" subscales were similarly high. More frequent monitoring (≥6 days/week vs. <4 days/week) was associated with higher satisfaction (p<0.001). According to participants, the best aspects of CGM use were the ability to see trends and graphs of glucose levels, detect low glucose levels and the ability to self-correct out of range levels. Barriers to CGM use cited included alarms, issues related to insertion sites and transmitter/receiver sizes and pain with sensor insertion.

4.2.1.3. Mixed population (adults and children) with T1DM

Seven parallel trials (8 publications) evaluating CGM versus SMBG in a mixed population of adults and children with T1DM met the inclusion criteria.[15,39,67,79,81,82,115,125] Children comprised between 22.5% and 51.6% of the trial populations. Notably, for one trial (JDRF 2008)[82] the mixed population reported here only includes 15-24 year olds (stratified data for the 8-14 year old pediatric population and >24 year old adults population are provided in the appropriate sections). Sample sizes ranged from 62 to 146 and the proportion of female participants ranged between 38% and 71%. Mean ages ranged from 18 to 33 years (total age range across trials was 8 to 72 years). The average duration of diabetes ranged from 8.4 to 18.7 years. In two trials reporting race, non-Hispanic white participants comprised of 90% and 94% of the populations. Mean baseline HbA1c values ranged from 6.4% to 9.6%. (Table 27). Across studies that included both children and adults, the majority had a roughly equal percentages of both (Table 28). Of the seven trials, five were industry funded (from sponsors Abbott Diabetes Care or Medtronic).

Three of the seven trials exclusively used CSII for insulin delivery. Participants in the remaining four trials used multiple daily injection or CSII for insulin delivery with a majority of participants using CSII (67%-86.3%) in all but one trial (48.1%). Study durations ranged from 3 months to 6 months. In all trials, participants were instructed to confirm CGM results in conjunction with SMBG for therapy decisions. Four of the seven trials were rated moderately low,[15,79,88,115] while the remaining three trials were rated with moderately high risk of bias.[39,67,125] The main methodological shortcomings included lack of assessor blinding in all six trials; unclear randomization and concealment procedures were issue in all the trials rated moderately high risk of bias, as well as unclear follow-up in one trial[125] and unclear control for potential confounders in the other.[39]

Table 27. Summary of patient characteristics for parallel RCTs and cross-over trials reporting on mixed adults and children with type 1 diabetes mellitus

Characteristics	Parallel Trials, n=7 (# of trials reporting/total)[15,39,67,79,81,82,115,125]	Battelino 2012/Hommel 2014[14,69]
Males, %	29%-62% (5/7)	51.6%
Age, years; mean	18.5-33.1 (6/7)	28
Non-hispanic white race, %	89.9%-93.8% (2/7)	NR
Total BMI, mean kg/m2	22.2-26.6 (3/7)	23.5
DM duration, years; mean	8.4-18.7 (6/7)	15
HbA1c%, mean	6.5-9.2% (7/7)	8.4

BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; NR: not reported; RCT: randomized controlled trial.
* Proportion of male and female participants, and mean ages for under 18 population not reported for Deiss 2006

Table 28 Proportion of children and adults in trials of mixed populations

Study, RoB	Children, % (n/N) [age range]	Adults, % (n/N) [age range]
Battelino 2011 *Moderately Low*	44.2% (53/120)[10-17 yrs]	53.8% (67/120) [18-65 yrs]
Deiss 2006 *Moderately High*	50% (81/162) [8-18.9 yrs]	50% (81/162) [19-59.5 years]
JDRF 2008* *Moderately Low*	34.2% (110/322) [15-24 yrs]* 35.4 (114/322) [<15 yrs]	30.4% (98/322) [>24]
JDRF 2009 *Moderately Low*	22.5 (26/129) [<15 yrs]25.6% (33/129) [15-24 yrs]	51.9% (67/129) [>24]
O'Connell 2009 *Moderately Low*	51.6% (32/62) [13-19 yrs]	48.4% (30/62) [19-40.0 yrs]
Raccah 2009 *Moderately High*	40% (46/115) [<19 yrs]	60% (69/115)[≥19 yrs]
Hirsch 2008 *Moderately High*	29% (40/138) [12-17.9 yrs]	71% (98/138) [18-72 yrs]

ROB: risk of bias; yrs: years
*Only the 15-24 year old population is reported in this section. The pediatric (≤14 years) and adult (>25 year olds) populations are reported in the appropriate sections.

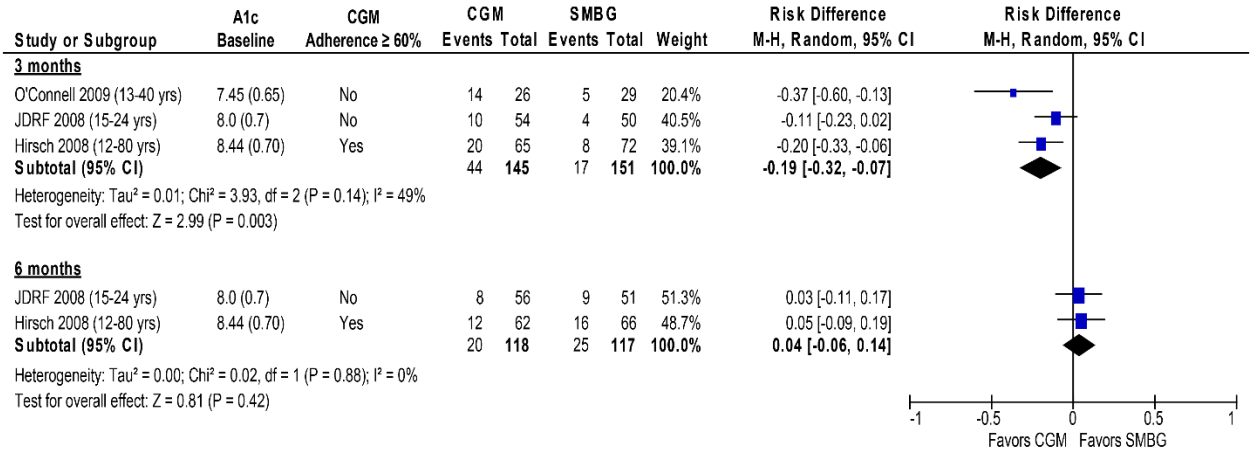
Primary Intermediate Outcomes

HbA1c %

Randomized controlled trials

Achieving HbA1cTarget: Across three parallel trials, significantly more patients in the CGM group achieved success compared with SMBG, defined as achieving HbA1C target of <7% at 3 months (3 trials, pooled RD -19%, 95% CI-32% to -7%, I^2=49%).[67,82,115] (Figure 28). At 6 months there was no difference between groups (2 trials, pooled RD 4%, 95% CI-6% to 14%, I^2= 0%) across two of the trials. [67,82]

Figure 28. CMG vs. SMBG from parallel RCTs in mixed population (children and adults): Proportion achieving HbA1c % of <7%



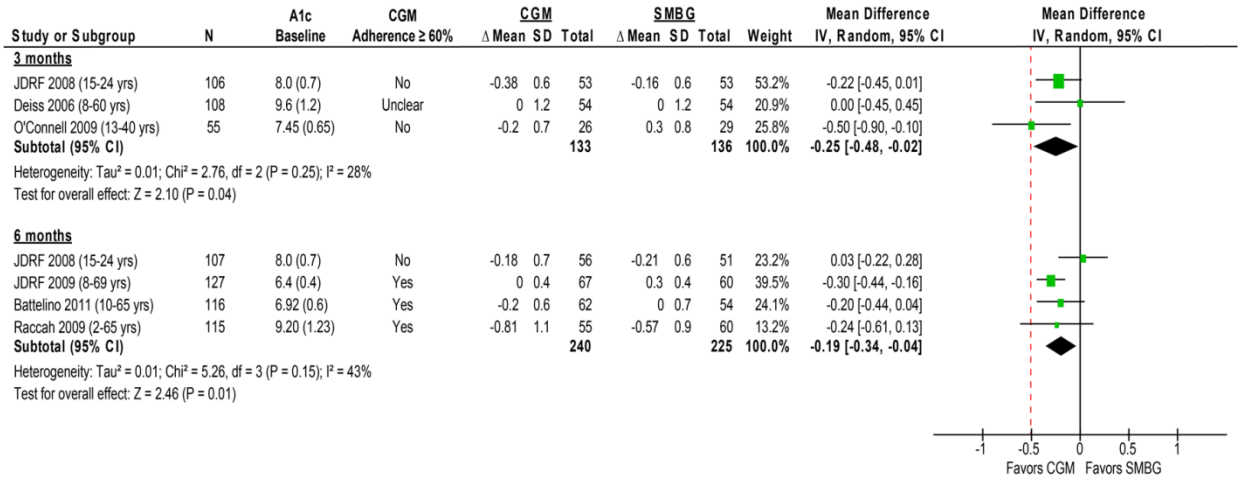
A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Absolute reduction (≥0.5% in HbA1c %) or relative reduction in HbA1c % (≥ 10% from baseline):
One trial reported no difference between CGM and SMBG in the proportion of patients experiencing an absolute reduction in HbA1c % of ≥0.5% at either 3 months (RD -14%, 95% CI-33% to 4%) or at 6 months (RD 2%, 95% CI-17% to 20%).[82] Similarly across the same trial, there were no differences in the proportion of patients experiencing a relative reduction in HbA1c % of ≥ 10% from baseline at 3 (RD -12%, 95% CI-27% to 2%) or at 6 months (RD -4%, 95% CI-17% to 8%).

Between group change in mean HbA1c % from baseline:
A small reduction from baseline mean HbA1c % favoring CGM was seen at 3 months across three parallel design RCTs[39,82,115] (3 trials, pooled MD in change scores -0.25%, 95% CI-0.48% to -0.02%%, I^2=28%) and across four parallel design trials at 6 months (4 trials, pooled MD in change scores -0.19%, 95% CI-0.34% to -0.04%, I^2=43%)[15,79,82,125] but may not be clinically significant (Figure 29). One cross-

over trial [15] reported lower HbA_{1c} % associated with CGM compared with SMBG. The mean difference in patients' HbA1c % comparing CGM to SMBG was -0.43 (-0.32 to -0.55) (p<0.001), Table 29.

Figure 29. CMG vs. SMBG in parallel RCTs in (children and adults): Between group difference in HbA1c % change from baseline



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Table 29. Summary of HbA1c % results from cross-over trials of CGM vs. SMBG in mixed populations

Author year, Treatment period ROB (N)	Timing	CGM Periods Mean ± SD	SMBG Periods Mean ± SD	MD (95% CI)	p-value
SWITCH Battelino 2012 Treatment periods: 6 months Washout phase: 4 months *Moderately Low* (N = 153)	Baseline	8.3 ± 0.7	8.5 ± 0.6	NR	NR
	Across both treatment periods*	8.04 ± NR	8.47 ± NR	-0.43 (-0.32 to -0.55)	<0.001

CGM: Continuous Glucose Monitoring; CI: confidence interval; F/U: follow-up; HbA1C: hemoglobin A1C; NR: not reported; RoB: risk of bias; SMBG: self-monitoring of blood glucose; SD: standard deviation

*The two groups were compared using ANOVA with adjustment for period effect and subject as random effect. Period was included in the model regardless of statistical significance. The mean difference in HbA1c between the Sensor On and Sensor Off arms, with the corresponding 95% CI and p value, were estimated.

Adherence

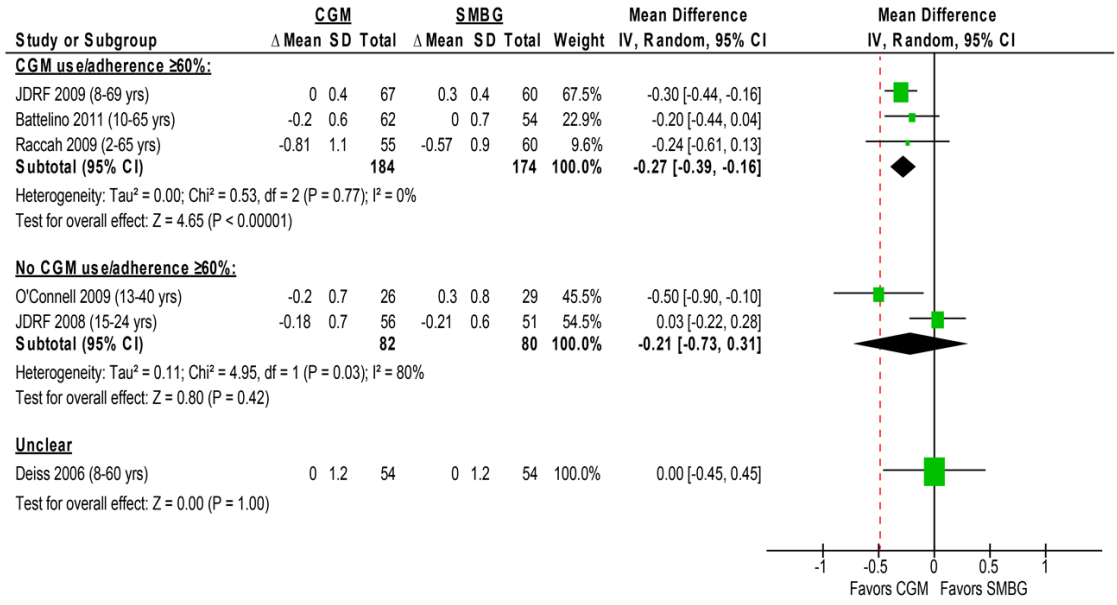
Trials evaluating the impact of sensor use suggest that, among those using CGM, greater adherence to sensor use was associated with improved mean HbA1c at follow-up (Table 30).[14,67,115,125] Based on our categorization of CGM use ≥60% of the time, the impact of adherence on differences between CGM versus SMBG in mean HbA1c % at final follow-up is unclear, however few trials reported adherence of <60% and substantial heterogeneity in those trials is noted (Figure 30).

Table 30. Sensor use (adherence) and change in HbA1c % from trials in mixed populations of adults and children with T1DM

Study, Follow-up *ROB*	CGM sensor adherence (n)	Mean HbA1c (%) at follow-up	P-value
Hirsch 2008 6 months *Moderately High*	<60% of the time (n=4)	mean change NR	referent
	60%–80% of the time (n=12)	mean change NR	adj. p=0.008*†
	80%–100% of the time (n=32)	mean change NR	adj. p=0.002*†
	>100% of the time (n=18)	mean change NR	adj. p=0.002*†
O'Connell 2009 3 months *Moderately Low*	≥70% of total study period (n=11)	6.7	adj. MD* -0.51 (95% CI -0.04, -0.98), p=0.04
	<70% of total study period (n=14)	7.4	
Raccah 2009 6 months *Moderately High*	CGM use ≥70% of the time (n=32)	mean change -0.96 ± 0.93 vs. SMBG (n=59) -0.55 ± 0.93	p=0.004 (difference NS when all 55 CGM patients included in analysis)
Battelino 2012 6 months *Moderately Low* Cross-over trial	≥70% of required time (n=110)	mean change -0.51 ± 0.07	≥70%: p<0.001 <70%: p=0.03 p for between group difference NR
	<70% of required time (n=43)	mean change -0.24 ± 1.11	

adj: adjusted; CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; NS: not statistically significant; ROB: risk of bias; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus
*Adjusted for baseline A1c values.
†Authors state that the effect of compliance was significant (p=0.046); each 1 point (10%) increase in compliance was associated with a 41% increase in the probability of a 0.5% reduction in A1C.

Figure 30. CGM vs. SMBG HbA1c % at longest follow-up stratified by CGM use of ≥60% of the time in mixed populations (children and adults)*



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years
*definition of use/adherence varied across trials; categorization for these analyses is provided in appendix

Observational studies

One observational study reported HbA1c results in CGM users only. This study, a follow-up study of the JDRF 2008 trial,[80] evaluated a mixed population of adults and children (n=51, age 15 to 24 years, with A1C ≥ 7%) who had been randomized initially to SMBG and who were offered CGM at the end of the trial for up to 26 weeks. HbA1c in this age group increased slightly from baseline 0.1 ± 0.7%, p=0.95, which is identical to what occurred during the RCT phase (i.e., during SMBG only). The proportion of adults and children with improvement of ≥0.5% and HbA1c % levels <7.0% was 25% and 11% respectively, following 6 months of CGM use during the non-randomized phase of the study.

Adherence in observational studies

Two prospective cohort studies, both follow-up studies of the JDRF 2008 trial, provided data on adherence; one reported adherence to CGM use during the trial (n=50, age ≥25 years)[77] and the other reported frequency of CGM use among those who had been randomized initially to SMBG and who were offered CGM at the end of the trial for up to 26 weeks (n=51, age ≥25 years with A1C ≥ 7%).[80] Both studies found that greater CGM adherence/use was associated with better HbA1c levels in a mixed adult and children population over 6 to 12 months of follow-up (Table 31). One of the JDRF extension studies[80] also reported the proportion of patients that improved HbA1c by ≥0.5% and who had levels <7% with similar results (Appendix G).

Table 31. Frequency of CGM use and change in HbA1C % levels among mixed populations (children and adults): observational studies

Study (year), Design, *RoB* Outcome	Group 1; Average use ≥ 6 days/week in month 6	Group 2; Average use 4–6 days/week in month 6	Group 3; Average use >0 to <4 days/ week in month 6	Group 4; Average use 0 days/week in month 6	P-value
JDRF 2010 Prospective cohort *High‡* Change in HbA1c %, age 15-24 years	0.0 ± 0.3 (n=12)	−0.6 ± 0.3 (n=7)	0.0 ± 0.5 (n=26)	+0.4 ± 1.2 (n=11)	0.01
JDRF 2009 Prospective cohort *High‡* Change in HbA1c, %, age 15-24 years	−0.48*	−0.08*	+0.02*		0.002†

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; SD: standard deviation
* Mean values were estimated from figure in article.
† p adjusted for baseline A1C.
‡Study was a case series; according to AAI SOP, risk of bias for a case series is assessed as high

Hypoglycemia (<70 mg/dL)

Randomized controlled trials

Across two parallel design RCTs,[15,67] there were no differences between CGM and SMBG in the mean number of hypoglycemic events hypoglycemia <70 mg/dL, the percent of time spent in that range in a third trial[115] or in a change from baseline in the number of events per day, [125] Table 32. There was no difference between CGM and SMBG groups with regard to number of minutes spent in the hypoglycemia range (<70 mg/dL) at 3 months (2 trials, pooled MD -12.3, 95CI -40.6 to 16.3 I^2=0%)[79,82], and a small difference favoring CGM at 6 months (4 trials, pooled RD -16.3, 95% CI-32.2 to -0.37 I^2=21%) (Figure 31) that is of questionable clinical significance.[15,79,82,125]

Table 32. Outcomes measuring hypoglycemia in a mixed population (adults and children) with T1DM from parallel trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n) or Median (IQR)	SMBG Mean ± SD (n) or Median (IQR)	MD (95% CI) Effect Size (SE)	p-value
Hypoglycemia events						
Battelino 2011 *Moderately Low*	Number of hypoglycemic events per day (<63 mg/dl)	Baseline	NR	NR	NR	NR
		6 months	0.53 ± 0.6 (n=62)	0.76 ± 0.94 (n=54)	Ratio of means 0.70 (0.43 to 1.03)	0.08
Hirsch 2008 *Moderately High*	Number of hypoglycemic events per patient per day (<70 mg/dl)	Baseline	0.83 ± 0.73 (n=72)	0.84 ± 0.73 (n=66)	NR	NR
		6 months	1.17 ± 0.74 (n=72)	0.88 ± 0.76 (n=66)	NR	0.071
O'Connell 2009 *Moderately Low*	% of time spent in hypoglycemic range ≤70 mg/dl (over 6 days at end of study)	Baseline	9.3 ± 5.9 (n=26)	10.3 ± 7.6 (n=29)	NR	NR
		3 months	9.2 ± 8.7 (n=26)	9.1 ± 6.9 (n=29)	MD 0.54 (-3.5 to 4.6)	0.79
Raccah 2009 *Moderately High*	Δ from baseline in # of hypoglycemic events per day (< 70 mg/dl)	Baseline	NR	NR	NR	NR
		6 months	0.1 ± 0.9 (n=46)	0.1 ± 0.7 (n=54)	MD 0.0 (-0.3% to 0.3%)*	1.0
Area under the curve (AUC)						
Battelino 2011 *Moderately Low*	AUC Hypoglycemia (<63 mg/dL)	Baseline	NR (n=62)	NR (n=58)	NR	NR
		6 months	5.4 ± 7.6 (n=62)	11.1 ± 14.2 (n=54)	NR	NR
JDRF 2009 *Moderately Low*	AUC Hypoglycemia (≤70 mg/dL)	Baseline	0.64 (0.19 to 1.24) (n=67)	0.60 (0.18 to 1.88) (n=62)	NR	NR
		3 months	0.32 (0.09 to 0.80) (n=67)	0.48 (0.17 to 1.80) (n=58)	NR	NR
		6 months	0.26 (0.11 to 0.64) (n=66)	0.49 (0.13 to 1.73) (n=60)	NR	0.03/0.01/0.008†

Hirsch 2008 *Moderately High*	AUC Hypoglycemia (<70 mg/dL)	Baseline	0.41	0.47	NR	NR
		6 months	0.32‡ (n=72)	0.78‡ (n=66)	0.4651 (0.1209)§	0.0002
Raccah 2009 *Moderately High*	Δ from baseline AUC Hypoglycemia (<70 mg/dL)	Baseline	NR (n=46)	NR (n=54)	NR	NR
		6 months	0.4 ± 1.3 (n=46)	0 ± 1.8 (n=54)	MD 0.4 (-0.2 to 1.0)*	0.21*

AUC, area under curve; CI, confidence interval; CGM, continuous glucose monitoring; IQR, interquartile range; MD, mean difference; mos, months; NR, not reported; OR, odds ratio; ROB, risk of bias; SE, standard error; SMBG, self-monitoring blood glucose; T1DM, type 1 diabetes mellitus

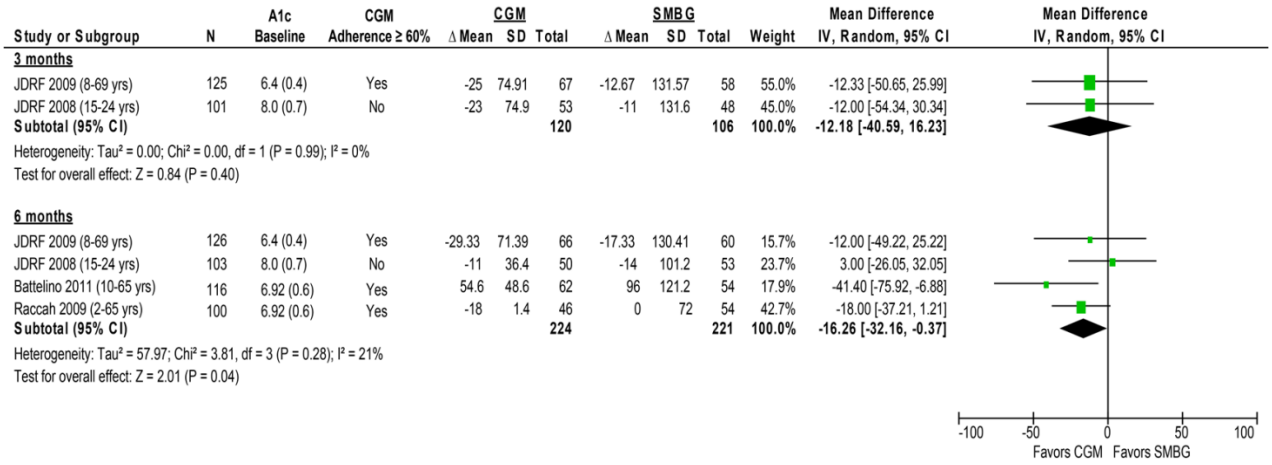
*Calculated by AAI

†*P* values were for 3 and 6 mos. combined from three methods: ANCOVA model based on van der Waerden scores, ANCOVA model with truncation of outliers, and ANCOVA model with square root transformation. P values calculated from 3 and 6 month data combined.

‡Value estimated from graph

§Least squares mean (standard error)

Figure 31. CMG vs. SMBG in parallel RCTs in mixed populations (children and adults); Minutes per day in the hypoglycemia range (<70mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Observational studies

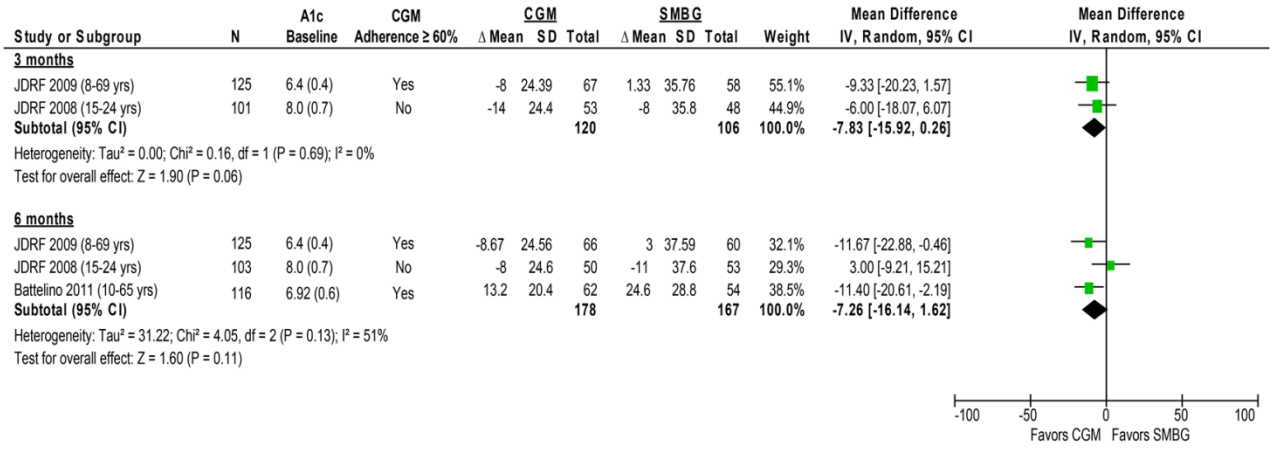
One of the observational studies reported on hypoglycemia in CGM users only. The study was a follow-up of the JDRF 2008 trial[80] which evaluated a mixed population of adults and children (n = 55, age 15-24 years) who had been randomized initially to SMBG and who were subsequently offered CGM at the end of the trial for up to 26 weeks. A statistically significant reduction from baseline to 6 months was seen in minutes per day spent in hypoglycemic range ≤70 mg d/l (mean 93 vs. 55, respectively, p=0.005) and ≤60 mg d/l (mean 49 vs. 23, respectively, p=0.001) in these patients.

Hypoglycemia (<55 mg/dL)

Randomized controlled trials

As reported by three parallel trials,[15,79,82] minutes per day in the hypoglycemia range <55 mg/dL tended to favor CGM versus SMBG at both 3 months (2 trials) and 6 months (3 trials), however the mean differences did not reach statistical significance at either timepoint (Figure 32).

Figure 32. CMG vs. SMBG in parallel RCTs in mixed populations (children and adults); Minutes per day in the hypoglycemia range (<55 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Observational studies

One follow-up study to the JDRF 2008 trial[80] reported on severe hypoglycemic episodes for CGM users only and reported a significant improvement from baseline to 6 months in minutes per day spent in hypoglycemic range ≤50 mg d/l (mean 19 vs. 4, respectively, p=0.008). This study evaluated a mixed population of children and adults (n=73, age 15-24 years) who had been randomized initially to SMBG were subsequently offered CGM at the end of the trial.

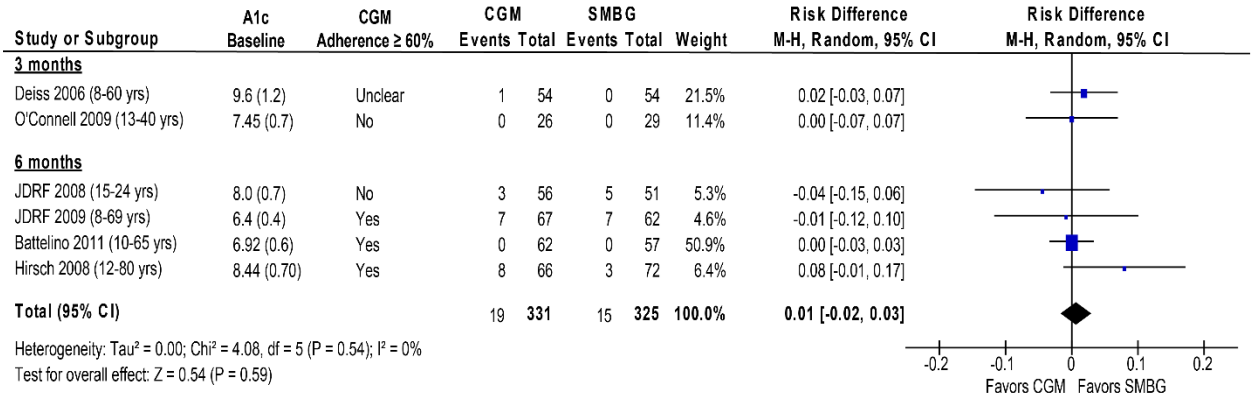
Severe Hypoglycemic Events

Randomized controlled trials

Across trials, there were no differences between CGM and SMBG in any measures of severe hypoglycemia at any time (Figures 33-35 and Table 33). Studies were likely underpowered to detect differences. In parallel RCTs, there were no differences between CGM and SMBG in the proportion of patients with ≥ 1 severe hypoglycemic events at any time frame (6 trials, pooled RD 1%, 95% CI-2% to 3%, I^2=0%) (Figure 31) or in the number of severe events (6 trials, pooled RD 1%, 95% CI-2% to 4%, I^2= 29%).[15,39,67,79,82,115] Similarly, there was no difference between groups in the number of severe hypoglycemic events with seizure, coma or loss of consciousness at 3 months (3 trials pooled RD 1%,

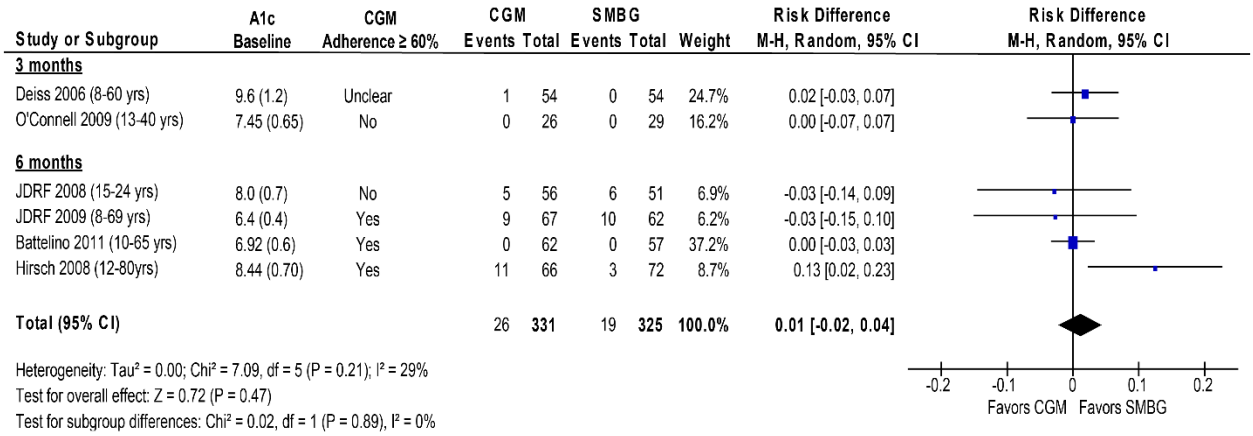
95% CI-3% to 4%, I^2= 9%).[79,82,125] Figure 32. In one cross-over trial, there was no difference between CGM phases and SMBG phases in the number or rate of severe hypoglycemic episodes requiring assistance from another or neurological recovery in response to restoration of plasma glucose to normal (p = 0.4).[14] Table 33. Studies were likely underpowered to detect differences in events between CMG and SMBG.

Figure 33. CMG vs. SMBG in parallel RCTs in mixed populations (children and adults): Proportion of patients with ≥ 1 severe hypoglycemic events



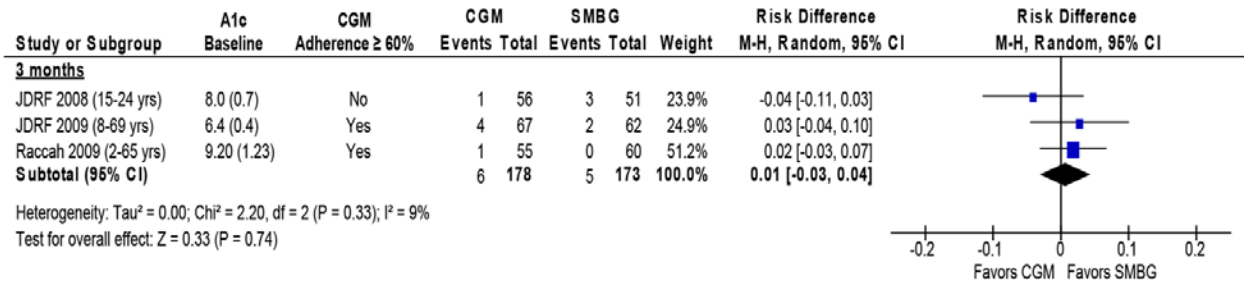
A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 34. CMG vs. SMBG in parallel RCTs in mixed populations (children and adults): Number of severe hypoglycemic events



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 35. CMG vs. SMBG in parallel RCTs in mixed populations (children and adults): Number of severe hypoglycemic events with seizure, coma or loss of consciousness



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Table 33. Incidence and number of events of severe hypoglycemia in a mixed population of adults and children with T1DM from parallel RCTs and cross-over trials of CGM vs. SMBG

Author year ROB	Outcome	Timing	CGM Mean ± SD (n)	SMBG Mean ± SD (n)	MD (95% CI) Effect Size (SE)	p-value
Parallel trials						
Battelino 2011 *Moderately Low*	Mean number of severe hypoglycemic events per day (<55 mg/dl)	6 mos	0.28±0.54 (n=62)	0.37±0.40 (n=54)	Ratio of means 0.76 (95% CI 0.47 to 1.43)	0.07
JDRF 2009 *Moderately Low*	Mean number of severe hypoglycemic events per day (<54 mg/dl for ≥20 minutes)	3+6 mos*	0.25±0.40 (n=67)	0.47±0.68 (n=62)	NR	0.07
Author year Treatment period length (ROB)	**Outcome**	**Timing**	**CGM Periods Mean ± SD or 95% CI (n)**	**SMBG Periods Mean ± SD 95% CI (n)**	**MD (95% CI) Effect Size (SE)**	**p-value**
Crossover trials						
SWITCH Battelino 2012 Treatment periods: 6 months Washout phase: 4 months *Moderately Low*	Episodes of acute/severe hypoglycemia†	Across both treatment periods‡	4 (5.7 per 100 patient-years)	2 (2.83 per 100 patient-years)	NR	0.40

CGM: Continuous Glucose Monitoring; CI: confidence interval; F/U: follow-up; HbA1C: hemoglobin A1C; mos: months; NA: not applicable; NR: not reported; SD: standard deviation; SMBG: self-monitoring of blood glucose;
*Data was collected during the week after the 13 and 26 week visits.
†Requiring assistance from another person or neurological recovery in response to restoration of plasma glucose to normal
‡The two groups were compared using ANOVA with adjustment for period effect and subject as random effect. Period was included in the model regardless of statistical significance.

Observational studies

One observational study reported on severe hypoglycemic episodes for CGM users only. The study was a follow-up of the JDRF 2008 trial[80] and evaluated a mixed population of children and adults (n=73, age 15-24 years) who had been randomized initially to SMBG and who were subsequently offered CGM at the end of the trial for up to 6 months. During the 6-month nonrandomized phase, there were three severe hypoglycemic events in three (4%) subjects, two of which resulted in seizure or loss of consciousness. The incidence rate was 8.2 per 100 person-years, which was much lower than the incidence rate during the previous 6-month control period of the RCT (22.3 per 100 person-years).

Nocturnal Hypoglycemia (<70 mg/dL, <63 mg/dL, <55 mg/dL,)

Nocturnal hypoglycemia was reported in one parallel trial.[15] CGM was associated with a lower mean number of excursions <63 mg/dL and <55mg/dL (Table 34).

Table 34. Nocturnal hypoglycemia in a mixed population of adults and children with T1DM from a parallel RCT trial of CGM vs. SMBG

Study *ROB*	Outcome	Timing	CGM Mean ± SD (n)	SMBG Mean ± SD (n)	MD (95% CI)	p-value
Battelino 2011 *Moderately Low*	No. of Hypoglycemic Excursions below <55 mg/dL	6 months	0.13 ± 0.30 (n=62)	0.19 ± 0.19 (n=54)	NR	p=0.01
	No. of Hypoglycemic Excursions below <63 mg/dL	6 months	0.21 ± 0.32 (n=62)	0.30 ± 0.31 (n=54)	NR	p=0.009

CGM: continuous glucose monitoring; CI: confidence interval; MD: mean difference; NR: not reported; ROB: risk of bias; SD: standard deviation; SMBG: self-monitoring blood glucose

Observational studies

One follow-up study to the JDRF 2008 trial[80] reported on nocturnal hypoglycemia in a mixed population of children and adults with type 1 diabetes (n=55, age 15-24 years) who had been randomized initially to SMBG and who were subsequently offered CGM at the end of the trial for up to 6 months. During the nonrandomized phase, a significant improvement from baseline to 6 months was reported in minutes per night spent in hypoglycemic range ≤70 mg d/l (mean 7 vs. 4, respectively) among CGM users but there was no change in duration of severe hypoglycemia (≤50 mg d/l), mean 0 vs. 0, respectively (p-values not reported).

Secondary Intermediate Outcomes

Hyperglycemia and DKA

Randomized controlled trials

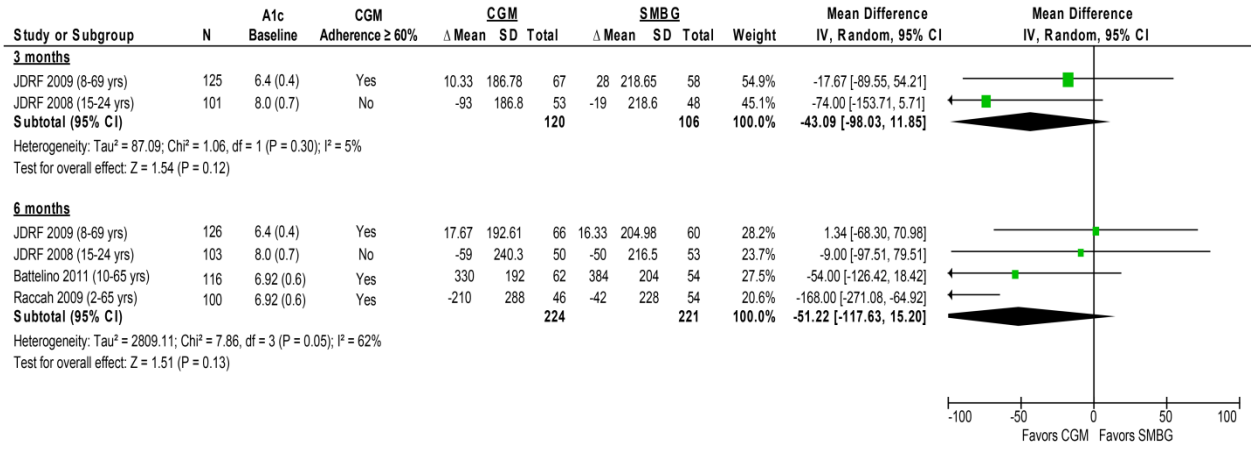
Across parallel trials, instability of effect size estimate precludes drawing firm conclusions for the time spent in hyperglycemic ranges. There was no clear difference between CGM and SMBG in adults with

regard to minutes spent in a hyperglycemic range (>180 mg/dL) across two trials at 3 months [79,82] or at 6 months across four trials,[15,79,82,125] (Figure 36). Substantial heterogeneity is noted for the 6 month pooled estimate (I^2=62%). At a threshold of >250 mg/dL, CGM was associated with a small reduction in time spent in the range at both 3 and 6 months as reported by three trials (Figure 37),[15,79,82] however the clinical significance of the differences is not clear for this indirect outcome.

Results were somewhat mixed across two parallel trials that reported area under the curve (AUC) at different hyperglycemic thresholds at 6 months (Table 35). One trial reported no difference between CGM and SMBG in AUC at >180mg/dL (p = 0.2913)[67] while the other reported a greater change from baseline for CGM (mean difference in change scores 2.796, p <0.05).[125] One crossover trial reported significant reduction in the average daily AUC >13.9 mmol/l per 24 hours during CGM phases compared with SMBG phases (p< 0.001) across both 6 month treatment phases.[14]

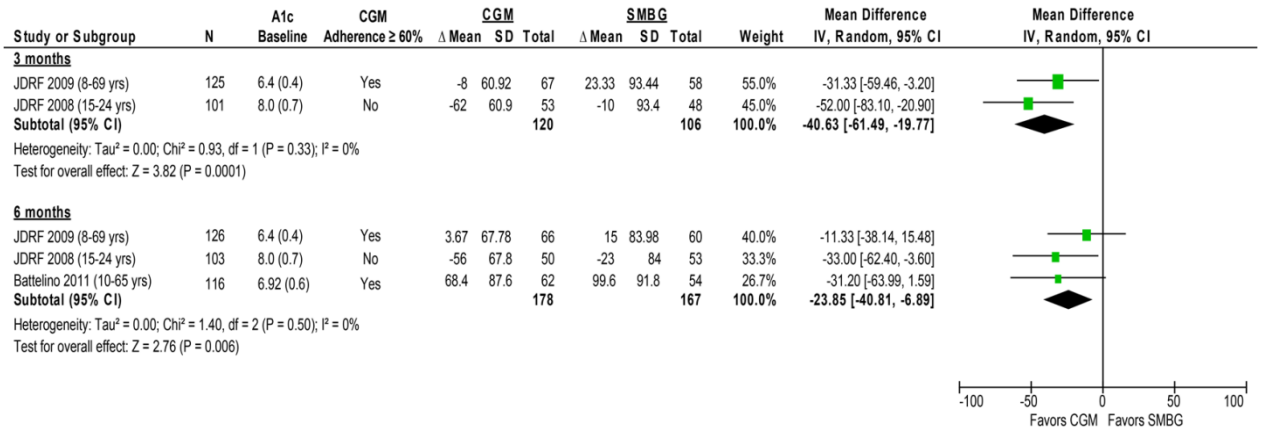
There was no difference between CGM and SMBG periods with regard to episodes of DKA in one cross-over trial (Table 35). [14]

Figure 36. CMG vs. SMBG in parallel RCTs in mixed populations (adults and children): Minute per day in hyperglycemic range (>180 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Figure 37. CMG vs. SMBG in parallel RCTs in mixed populations (adults and children): Minute per day in hyperglycemic range (>250 mg/dL)



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years

Table 35. Hyperglycemia or DKA in mixed populations (adults and children) with T1DM from parallel RCTs or cross-over trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM Mean ± SD (n)	SMBG Mean ± SD (n)	MD (95% CI) Effect Size (SE)	p-value
Parallel trials						
Hirsch 2008 *Moderately High*	AUC Hyperglycemia (>180 mg/dL)	Baseline	33.0	35.0	NR	NR
		6 mos (Δ from baseline)	-9.7 ± 16.5 (n=66)	-11.3 ± 19.3 (n=72)	Adj MD 2.80 (NR)	0.29
Raccah 2009 *Moderately High*	AUC Hyperglycemia (>190 mg/dL)	Baseline	NR	NR	NR	NR
		6 mos (Δ from baseline)	-17.1 ± 31.7 (n=46)	-5.8 ± 26.7 (n=54)	MD -11.3 (-22.9 to 0.29)*	p<0.05

Author year ; treatment period length (ROB)	Outcome	Timing	CGM Periods Mean ± SD or 95% CI (n)	SMBG Periods Mean ± SD 95% CI (n)	MD (95% CI) Effect Size (SE)	p-value
Crossover trials						
SWITCH Battelino 2012 Treatment period: 6 mos Washout: 4 mos *Moderately Low*	Average daily AUC >10.0 mmol/l† per 24 hours, median (IQR)	Across both treatment periods	4039 (2304 to 7665)	6097 (3731 to 9829)	NR	<0.001
	Average daily AUC >13.9 mmol/l† per 24 hours, median (IQR)	Across both treatment periods	722 (210 to 2,043)	1,362 (548 to 3,242)	NR	<0.001
		Baseline	NR	NR	NR	NR

Author year ; treatment period length (ROB)	Outcome	Timing	CGM Periods Mean ± SD or 95% CI (n)	SMBG Periods Mean ± SD 95% CI (n)	MD (95% CI) Effect Size (SE)	p-value
	Episodes of DKA	Across both treatment periods	2/153 (1%)	4/153 (3%)	NR	0.47

CGM: Continuous Glucose Monitoring; CI: confidence interval; F/U: follow-up; HbA1C: hemoglobin A1C; SMBG: self-monitoring of blood glucose; SD: standard deviation; CI: confidence interval; NR: not reported; AUC: area under the curve; DKA: diabetic ketoacidosis

*The two groups were compared using ANOVA with adjustment for period effect and subject as random effect. Period was included in the model regardless of statistical significance. The mean difference in HbA1c between the Sensor On and Sensor Off arms, with the corresponding 95% CI and p value, were estimated.

†13.9 mmol/l converts to 250 mg/dL

Observational studies

One observational study reported on hyperglycemia in CGM users only. The study was a follow-up of the JDRF 2008 trial[80] and evaluated a mixed population of adults and children (n=55, age 15-24 years) who had been randomized initially to SMBG and who were subsequently offered CGM at the end of the trial for up to 6 months. A statistically significant improvement from baseline to 6 months was reported for minutes per day spent in hyperglycemic range >180 mg d/l (mean 494 vs. 582, respectively, p=0.03) during CGM use; the difference for severe hyperglycemic (>250mg d/l) did not reach statistical significance (mean 166 vs. 210, respectively, p<0.07) in this population.

Health-related quality of life

None of the included RCTs or observational studies reported quality of life in mixed populations of children and adults with T1DM.

4.2.2. Type 2 Diabetes Mellitus (T2DM)

The general findings for T2DM for the primary clinical and intermediate outcomes are briefly summarized below. Detailed findings (including results for secondary outcomes) are then presented. For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. No trials using newer CGM devices were identified in this population. The majority of the trials were moderately high risk of bias (see Appendix E). The overall strength of evidence for most efficacy outcomes was considered low across interventions and comparators. In general, if effect estimates tended to favor one treatment but failed to reach statistical significance with confidence interval crossing the null value of zero or one (perhaps due to sample size), the results are interpreted as showing no clear difference between treatments. If effect estimates are very close to zero and not statistically significant, results are interpreted as no difference between groups.

Summary of results

Adults with T2DM

One of the four trials of traditional CGM in this population used newer CGM technology. One trial of flash CGM was included. Mean baseline HbA1c% values for all trials were ≥ 8.3%

Primary clinical outcomes

Trials reporting primary clinical outcomes were not identified.

Primary intermediate outcomes:

HbA1C %

- Traditional CGM: In one trial using newer devices, achieving HbA1c % of <7% was more common in adults with CGM use versus SMBG at 3 months but failed to reach statistical significance; no differences between groups was seen at 6 months. Significantly more CGM patients achieved ≥0.5% reduction in HbA1c at 3 and 6 months, however. (SOE Low for both outcomes and time points) More CGM patients achieved a clinically and statistically significant reduction from baseline in mean HbA1c % favoring CGM over SMBG at 3 months (3 trials, SOE Moderate). At 6 months the difference was statistically significant but may not be clinically significant. (3 trials, SOE Low); the difference was not statistically significant at 9.5 and 12 months in one small trial (SOE Insufficient at 9, 12 months). Effect estimates from the trial incorporating newer devices were somewhat smaller, but generally consistent with those using older technology.
- Flash CGM: There was no difference between FCGM and SMBG at 6 months. (SOE Insufficient)

Hypoglycemia

- **Severe hypoglycemic events:** Studies were likely underpowered to detect differences.
  - Traditional CGM**:** Severe hypoglycemic events were rare as reported by two trials. There was no difference between CGM and SMBG with regard to the proportion of patients experiencing an episode of severe hypoglycemia over 3 and 6 months follow-up in two trials; data were generally poorly reported for this outcome (SOE Low).
  - Flash CGM: Severe hypoglycemic events were rare and not different between groups. (SOE Insufficient)
- **Hypoglycemia (<55 mg/dL)**:
  - Traditional CGM: No between-group differences were reported for minutes per day, % of readings per day, or % of time spent in the <50 mg/dL range in two trials, one of which used newer technology or at 6 months in this later trial. (SOE Low).
  - Flash CGM: Significantly fewer minutes per day were spent in hypoglycemic range <55 mg/dl in the FCGM vs. SMBG group. (SOE Insufficient)

- **Hypoglycemia (<70 mg/dL)**
  - Traditional CGM: No between-group differences were reported for minutes per day, % of readings per day, or % of time spent in the <70 mg/dL range in two trials, one of which used newer technology at 3 months or at 6 months in this later trial. (SOE Low).

- Flash CGM: Significantly fewer minutes per day were spent in hypoglycemic range <70 mg/dl in the FCGM vs. SMBG group. (SOE Insufficient)

- **Nocturnal hypoglycemia**
  - Traditional CGM: No between-group differences were reported for minutes per day, % of readings per day, or % of time spent in the <70 mg/dL range in two trials, one of which used newer technology at 3 months or at 6 months in this later trial. (SOE Low).
  - Flash CGM: Significantly fewer minutes per night were spent in hypoglycemic ranges <55 and <70 mg/dl in the CGM vs. SMBG group.

Other outcomes (strength of evidence not assessed, see section below and appendices for details)

- **Adherence:** Greater sensor usage was associated with greater reduction in HBA1c% up to 12 months in one trial.
- **Quality of life and satisfaction:** No differences were found between traditional CGM and SMBG in any of the quality of life measures assessed in the one trial which employed newer devices, in another trial of older devices or for most measures used in the trial of flash CGM. CGM usage was associated with improved satisfaction in trials of traditional CGM and flash CGM.

Studies included

We identified five parallel-arm RCTs (across publications)[17,45,58,147,149,154,163] evaluating the use of real-time CGM in adults with type 2 diabetes mellitus that met inclusion criteria. One of these trials (REPLACE) utilized a novel form of CGM known as Flash glucose-sensing technology (Freestyle Libre, Abbott Diabetes Care) and will be reported distinct from the rest of the trials.[58]

Across the four trials that used traditional CGM,[45,147,149,154,163] sample sizes ranged from 57 to 158; mean ages were similar (range 56-60 years), males comprised 42% to 64% of the populations, and mean BMI ranged from 25 to 36 kg/m^2 across the trials (Table 36). Two of the trials[149,163] reported the mean duration of diabetes (12.5 and 17.2 years) while another reported median duration of 17.5 years[17]; in the remaining trials, patients were required to have had a diagnosis of type 2 diabetes for at least 3 months but no further information was provided. One trial was conducted specifically in military beneficiaries from Walter Reed Health Care Systems.[45,154] Only one trial reported on race and ethnicity, with non-Hispanic whites comprising 63% of the total population.[17] Inclusion criteria differed across the trials, with one[149] requiring that patients were currently being treated with insulin (either alone or in combination with oral antihyperglycemic agents), two[17,163] enrolling patients using either insulin or oral hypoglycemic agents (or a combination of the two), and the third trial[45,154] requiring that all patients that were being treated with diet and exercise alone or other glucose lowering therapies except prandial insulin. HbA1c requirements for inclusion also varied somewhat with one trial requiring levels between 7.5% and 10%,[17] one between 8.0% and 10%,[163] one between 7.0% and 12%,[154] and the fourth at least 7.0%; at baseline HbA1c ranged from 8.2% to 8.9% across the trials. All trials compared CGM to SMBG, although the trials based therapy modifications off of different criteria. Follow-up duration ranged from 2 to 12 months, and duration of CGM device use ranged from 2 to 6 months. Only one trial[147,149] reported that patients were specifically trained in the use of the CGM device.

Two trials were considered moderately low risk of bias.[17,163] The main methodological concern was a lack of blind assessment by the assessors and unclear controlling for confounding in the trial by Yoo et al. 2008. The other three trials were all were considered moderately high risk of bias. Common methodological concerns across these trials included unclear concealment of group allocation, lack of assessor blinding, and differential loss-to-follow-up (≥10% difference between between groups). One of the trials was directly funded by industry (DexCom)[45,154] and the other two received supplies or other assistance from device manufacturers (Abbott Diabetes Care and Medtronic Korea).

In addition to these trial of traditional CGM, we identified one parallel trial that evaluated flash CGM (FCGM) in adults with type 2 diabetes mellitus that met our inclusion criteria.[58] The study randomized 224 patients into groups that received flash glucose monitoring (n=149) using the Freestyle Libre Flash system or SMBG (n=75). Across the total population, participants predominantly used MDI, with CSII use at 5% in each group. The mean ages were 59 and 59.5 years old in the flash glucose monitoring group and SMBG group, respectively. The population was 94% white and 33% male, with a mean BMI of 33.2 kg/m2. Baseline HbA1c was 8.8% and mean duration of diabetes was 17.5 years. (Table 36)

Prior to randomization, the trial had a two week run-in period during which patients wore a flash glucose monitor in masked mode. During the run-in period, patients who had worn the device for less than 50% of the required time were excluded from further participation of the trial. No specific training was given to the intervention group. The trial was rated as moderately high risk of bias, with the main methodological shortcomings being lack of blind assessment, lack of concealed allocation and a between group attrition rate greater than 10%.

Table 36. Summary of patient characteristics for parallel RCTs reporting on adults with type 2 diabetes mellitus

Characteristics	Parallel trials, n=4 (# of trial reporting/total)[17,45,149,163]	Flash Glucose (Haak 2016)[58]
Males, n (%)	42%-64%(4/4)	33%
Age, years; mean (SD)	56.1-60, (4/4)	59.25 (10.25)
Non-hispanic white race, %	63% (1/4)	94%
Total BMI, mean (SD)	25.4-36 (4/4)	33.2(6.0)
DM duration, years; mean (SD)	12.5-17.2 (2/4), median 17.5 (1/4)	17.5 (8.0)
HbA1c%, mean (SD)	8.2-8.9 (4/4)	8.8(0.98)
Insulin dose, units/kg/day; mean	1.1(0.55) (1/4)	Basal:41.35 Bolus: 52.65
Basal Insulin, n/N%	33%* (1/4)	NR
Prandial Insulin, %	NR (0/4)	NR
Other DM Medications, n (%)	40.3%-68% (3/4)	NR
Severe hypoglycemia within 12 mos (%)	NR (0/4)	NR

BMI: body mass index; DM: diabetes mellitus; HbA1c: hemoglobin A1c; NR: not reported; RCTs: randomized control trials; SD: standard deviation;

* In Ehrhardt/Vigersky, 33% of patients used basal alone or in combination with oral medications. The other studies did not report proportions of basal insulin use.

Primary Clinical Outcomes

None of the trials in adults with Type 2 DM provided data on any of the primary clinical outcomes.

Primary Intermediate Outcomes

HbA1c %

Randomized controlled trials

Achieving HbA1c % target (<7.0%)

While more patients in the CGM compared with the SMBG group achieved HbA1c levels of <7.0% at 3 months in one trial (adjusted risk difference 10%),[17] the difference was not statistically significant; at 6 months the results were similar in both groups (Table 37).

Absolute reduction (≥0.5% in HbA1c %) or relative reduction in HbA1c % (≥ 10% from baseline):

Significantly more subjects using CGM compared with SMBG achieved both an absolute (≥0.5%) and a relative (≥10%) reduction from baseline in HbA1c % at 3 months (adjusted risk difference 31% and 25%, respectively) and 6 months (adjusted risk difference 26% and 22%, respectively) in one trial[17] (Table 37). Confidence intervals were wide.

Table 37. Target HbA1c <7.0%, absolute reduction of ≥0.5% and a relative reduction of ≥10% from baseline in HbA1c %: Adults with T2DM from Beck 2017.

Author year *ROB*	Outcome	Timing	CGM % (n/N)	SMBG % (n/N)	Adjusted RD (95% CI)*
Beck 2017[b] DIAMOND *Moderately Low*	**HbA1c <7.0%**	3 months	22% (17/77)	12% (9/75)	10% (−2% to 23%)
		6 months	14% (11/79)	12% (9/79)	3% (−9% to 14%)
	Absolute reduction of ≥0.5% in HbA1c %	3 months	79% (61/77)	51% (38/75)	31% (5% to 57%)
		6 months	73% (56/79)	49% (37/75)	26% (0% to 50%)
	Relative reduction of ≥10% in HbA1c %	3 months	57% (44/77)	35% (26/75)	25% (3% to 46%)
		6 months	52% (40/79)	32% (24/79)	22% (0% to 42%)

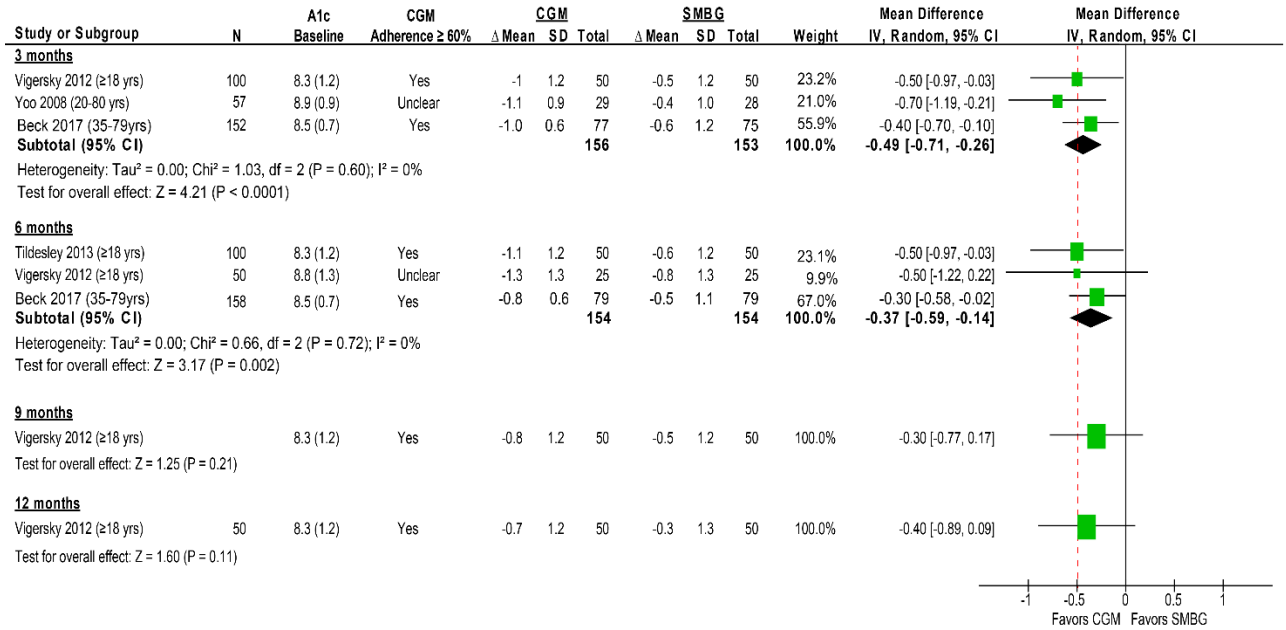
CGM: continuous glucose monitoring; CI: confidence interval; HbA1c: hemoglobin A1c; RD: risk difference; ROB: risk of bias; SMBG: self-monitoring of blood glucose; T2DM: type 2 diabetes mellitus.

*mixed-effects logistic regression models adjusting for baseline HbA1c level and accounting for clinical site.

Between group change in mean HbA1c % from baseline: Across four RCTs using traditional CGM, a statistically significant reduction from baseline in mean HbA1c % favoring CGM versus SMBG was seen at 3 months (3 trials, pooled MD in change -0.49%, 95% CI -0.71% to -0.26%, I^2=0%)[17,154,163] and 6 months (3 trials, pooled MD in change -0.37%, 95% CI -0.59% to -0.14%, I^2 = 0%),[17,149,154] Figure 38; only the 3 month estimate was clinically significant. One of these trials also reported a small reduction in mean HbA1c % from baseline at 9.5 months (MD in change -0.30%, 95% CI -0.77% to 0.17%) and at 12 months

(MD in change -0.40%, 95% CI -0.89% to 0.09%), however the differences did not reach statistical significance and may not be clinically meaningful.

Figure 38. CMG vs. SMBG in RCTs in adults with T2DM: Between group difference in HbA1c % change from baseline



A1c: hemoglobin A1c, %; CGM: continuous glucose monitoring; CI: confidence interval; DKA: diabetic ketoacidosis; RCTs: randomized controlled trials; SD: standard deviation; SMBG: self-monitoring of blood glucose; yrs: years.

One RCT evaluating flash CGM (FCGM)[58] found no difference between FCGM (mean 8.37% ± 0.83%) and SMBG (mean 8.34% ± 1.14%) in mean HbA1c % at 6 months after adjustment for baseline values: adjusted mean difference 0.03 (standard error [SE] 0.114), p=0.822.

Adherence

Only one of these trials explored whether adherence to sensor usage in the CGM group was associated with changes in HbA1c levels. [154] When compared with patients who wore the sensor less than 48 days, those who wore the sensor for 48 days or more (study protocol cut-off) showed a greater reduction from baseline in mean HbA1c at all timepoints measured (Table 38). In multivariate regression analyses which included time, age, sex, baseline therapies, and initiation of insulin during the study, the average decrease in HbA1c was greater in those who wore the CGM device per protocol: -1.31% with 48 days or more usage (p<0.0001) versus -0.76 with less than 48 days usage (p=0.008). The authors indicate that for each single day of CGM use over the course of the study, HbA1c decline by 0.02% (p=0.02).

Table 38. Change in HbA1c % based on CGM adherence in adults with T2DM in Vigersky 2012.

Follow-up	CGM sensor adherence	Unadjusted mean change in HbA1c (%) ± SD	Adjusted* mean change in HbA1c (%)
3 months	≥48 days (n=34)	-1.2 ± 1.1	-1.0
	<48 days (n=16)	-0.6 ± 1.1	-0.7
6 months	≥48 days (n=34)	-1.5 ± 1.5	-1.2
	<48 days (n=16)	-0.6 ± 1.5	NR†
9.5 months	≥48 days (n=34)	-1.1 ± 1.7	-1.3
	<48 days (n=16)	-0.2 ± 1.5	NR†
12 months	≥48 days (n=34)	-1.0 ± 1.5	-1.3
	<48 days (n=16)	-0.3 ± 1.3	NR†

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; SD: standard deviation; T2DM: type 2 diabetes mellitus

*Adjusted for age, sex, baseline therapies (diet and exercise only, oral medications only, oral medications plus exenatide, or basal insulin alone or in combination) and initiation of basal and/or prandial insulin during the study period.

†Data was not provided after 3 months; authors simply state that there was no further decline in HbA1c in this subgroup of CGM patients for the duration of the trial.

Hypoglycemia (<70 mg/dl, <50 mg/dl)

Randomized controlled trials

One trial[17] found no difference between CGM and SMBG at both 3 and 6 months for minutes per day or the percent of time during monitoring spent in hypoglycemic range <70 mg/dl or for area above the curve of 70 mg/dl (Table 39). However, compared with SMBG, the CGM group did show improvement from baseline at both timepoints for minutes per day in range <70 mg/dl. The authors state that biochemical hypoglycemia, measured with CGM, was infrequent, limiting the trial's ability to adequately assess the effect of CGM on reducing hypoglycemia. A second trial[45,154] reported the percentage of the total number of SMBG readings obtained in the CGM and the SMBG groups that were within the glucose range of <70 mg/dl and found no difference between groups at 3 and 12 months.

Similarly, in both trials, no significant differences between groups were seen for any outcome or timepoint when a hypoglycemic range of <50 mg/dl was considered (Table 39).

A third trial reported the amount of time spent in hypoglycemia range of <60 mg/dl in the CGM group but did not report this data for the SMBG group[163]; compared with when the CGM device was first used, the time spent in hypoglycemia was mildly increased when used last 2 months later, however, the difference was not statistically significant (p=0.10; data not reported).

Table 39. Hypoglycemia in adults with T2DM from trials of CGM vs. SMBG

Author year *ROB*	Outcome	Timing	CGM	SMBG	p-value
Beck 2017[b] DIAMOND *Moderately Low*	**Minutes per day in range <70 mg/dl,** median (IQR)	Baseline	11 (1-33) (n=79)	12 (3-39) (n=78)	ns
		3 months	9 (1-25) (n=77)	11 (0-37) (n=74)	ns
		6 months	4 (0-17) (n=74)	12 (0-34) (n=72)	ns
	% of time in range <70 mg/dl, median (IQR)	Baseline	0.6 (0-2.0) (n=79)	0.6 (0-2.6) (n=78)	ns
		3 months	0.3 (0-1.5) (n=77)	0.6 (0-2.3) (n=74)	ns
		6 months	0.3 (0-1.0) (n=74)	0.3 (0-2.3) (n=72)	ns
	Area above the curve of 70 mg/dl, median (IQR)	Baseline	0.1 (0-0.3) (n=79)	0.1 (0-0.3) (n=78)	ns
		3 months	0 (0-0.1) (n=77)	0 (0-0.3) (n=74)	ns
		6 months	0 (0-0.1) (n=74)	0 (0-0.2) (n=72)	ns
	Minutes per day in range <50 mg/dl, median (IQR)	Baseline	0 (0-8) (n=79)	0 (0-7) (n=78)	ns
		3 months	0 (0-0) (n=77)	0 (0-3) (n=74)	ns
		6 months	0 (0-1) (n=74)	0 (0-5) (n=72)	ns
	% of time in range <50 mg/dl, median (IQR)	Baseline	0 (0-0.2) (n=79)	0 (0-0.2) (n=78)	ns
		3 months	0 (0-0) (n=77)	0 (0-0) (n=74)	ns
		6 months	0 (0-0) (n=74)	0 (0-0.3) (n=72)	ns
Ehrahrdt 2011/Vigersky 2012 *Moderately High*	**% of SMBG reading per day in range <70 mg/dl,** mean	3 months	3.6% (n=44)	2.7% (n=47)	ns
		12 months	3.6% (n=44)	2.5% (n=48)	ns
	% of SMBG reading per day in range <50 mg/dl, mean	3 months	1.9% (n=44)	2.7% (n=47)	ns

CGM: continuous glucose monitoring; IQR: interquartile range; SMBG: self-monitoring blood glucose; T2DM: Type 2 diabetes mellitus.

One RCT (REPLACE) evaluating FCGM[58] found that patients using FCGM spent significantly fewer minutes per day in hypoglycemic range <70 mg/dl (adjusted mean difference: -28.2 minutes, SE 8.0, p=0.0006) and <55 mg/dl (adjusted mean difference -13.2 minutes, SE 4.1; p=0.0014) compared with SMBG at 6 months after adjustment for baseline values, equating to a reduction of 43% and 53%, respectively, for FCGM compared with SMBG in the time spent in hypoglycemia. Results were also significant favoring FCGM when the number of events and the area under the curve (AUC) for the respective hypoglycemic ranges were considered (see Appendix G for details).

Observational studies

During the open-label phase of the REPLACE trial,[59] patients initially randomized to FCGM were followed for an additional 6 months. Significant reductions from baseline to 12 months were seen in minutes per day spent in hypoglycemic ranges <70 mg/dl (mean change -42 ± 111 minutes, p=0.0002) and <55 mg/dl (mean change -24 ± 65.4 minutes, p=0.0002), corresponding to a reduction of 50% and 62%, respectively, in time spent in hypoglycemia. The number of events and the AUC for both hypoglycemia ranges were also significantly reduced from baseline to 12 months (see Appendix G for details).

Severe Hypoglycemic Episodes

Randomized controlled trials

No episodes of severe hypoglycemia, defined as an event requiring assistance from another person, were reported in either the CGM or SMBG group over 6 months in one trial.[17]

Two trials did not define severe hypoglycemia; one stated that no clinically symptomatic hypoglycemic events occurred over 3 months[163] and the other reported that severe hypoglycemia in both the CGM and SMBG group was negligible with no serious events over 6 months (data not provided).[149]

One RCT evaluating FCGM[58] reported a similar frequency of severe hypoglycemic events (i.e., an event requiring assistance from another person) in both groups: FCGM (2%; 3 patients with 1 event each) and SMBG (1%, 1 patient).

Nocturnal Hypoglycemia (<70 mg/dl, <50 mg/dl)

Randomized controlled trials

One trial[17] found no difference between CGM and SMBG for the percent of time during monitoring spent in hypoglycemic range <70 mg/dl (3 and 6 months: median 0 vs. 0) or for area above the curve of 70 mg/dl (3 and 6 months: median 0 vs. 0). Similarly, percent of time spent in hypoglycemic range <50 mg/dl did not differ between groups (3 months: median 0.2 vs. 0, respectively; and 6 months: median 0 vs. 0).

One RCT (REPLACE) evaluating FCGM[58] found that patients using FCGM spent significantly fewer minutes per night (within 7 hours) in hypoglycemic range <70 mg/dl (adjusted mean difference: -7.2 minutes, SE 2.4, p=0.003) and <55 mg/dl (adjusted mean difference -17.4 minutes, SE 4.8; p=0.0001) compared with SMBG at 6 months after adjustment for baseline values, equating to a reduction of 58% and 54%, respectively, for FCGM compared with SMBG in the time spent in nocturnal hypoglycemia. Results were also significant favoring FCGM when the number of nightly events for the respective hypoglycemic ranges were considered (see Appendix G for details).

Observational studies

During the open-label phase of the REPLACE trial,[59] patients initially randomized to FCGM were followed for an additional 6 months. Significant reductions from baseline to 12 months were seen in minutes per night (within 7 hours) spent in hypoglycemic ranges <70 mg/dl (mean change -18.6 ± 50.4 minutes, p=0.0002) and <55 mg/dl (mean change -11.4 ± 34.2 minutes, p=0.0008), corresponding to a reduction of 52% and 62%, respectively, in time spent in nocturnal hypoglycemia. The number of events and the AUC for both hypoglycemia ranges at night were also significantly reduced from baseline to 12 months (see Appendix G for details).

Secondary Intermediate Outcomes

Hyperglycemia (>180 mg/dl, >240 mg/dl)

Randomized controlled trials

One trial[17] found a greater reduction in minutes per day spent in the hyperglycemic range >180 mg/dl in the CGM group compared with the control group (p value for between groups not reported): the CGM group decreased from a median of 612 (IQR 411-809) minutes at baseline to 501 (IQR 323‑746) and 549 (IQR 353‑789) minutes at 3 and 6 months, respectively; corresponding values in the SMBG group were 607 (IQR 392‑775), 560 (382‑818), 571 (422‑883) minutes. The percentage of monitoring time spent above 180 mg/dl was also assessed in this trial with the CGM group showing a greater, but small and likely not statistically significant, decrease from baseline over 6 months compared with the SMBG group (CGM: 42%, 38%, and 35% at baseline, 3 months, and 6 months; SMBG: 41% vs. 41% vs, 40%, respectively). A second trial[154] reported the percentage of the total number of SMBG readings obtained in the CGM and the SMBG groups that were >180 mg/dl with no differences between groups, respectively, at 3 months (24.3% vs. 28.7%) or 12 months (23.1% vs. 28.6%).

One trial[17] found no clear difference between CGM and SMBG in minutes per day spent in the hyperglycemic range >250 mg/dl, although the CGM group showed a slightly greater reduction from baseline: the CGM group decreased from a median of 150 (IQR 68-265) minutes at baseline to 100 (IQR 37-180) and 105 (IQR 37‑246) minutes at 3 and 6 months, respectively; corresponding values in the SMBG group were 154 (IQR 66‑281), 137 (IQR53‑251), and 118 (IQR 48‑288) minutes. The results for the percentage of monitoring time spent above 250 mg/dl also did not differ between the groups. A second trial[154] reported the percentage of the total number of SMBG readings obtained in the CGM and the SMBG groups that were >240 mg/dl with no differences between group, respectively, at 3 months (7.4% vs. 12.1%) or 12 months (6.9% vs. 10.8%).

One RCT (REPLACE) evaluating FCGM[58] found no difference between the FCGM and SMBG groups with regards to minutes per day in hyperglycemic range >180 mg/dl (adjusted mean difference: 18 minutes, SE 37.8, p=0.597) and >240 mg/dl (adjusted mean difference: 6 minutes, SE 27.6; p=0.873) at 6 months after adjustment for baseline values.

Observational studies

During the open-label phase of the REPLACE trial,[58] patients initially randomized to FCGM were followed for an additional 6 months. No difference was seen between baseline and 12 months in minutes per day spent in hyperglycemic ranges >180 mg/dl (mean change 37.2 ± 296.4 minutes, p=0.198) and >240 mg/dl (mean change 1.8 ± 190.2 minutes, p=0.953), corresponding to a reduction of 7.2% and 1%, respectively (see Appendix for details).

Diabetic Ketoacidosis (DKA)

Randomized controlled trials

Two trials, one evaluating traditional CGM[17] and one evaluating FCGM,[58] no episodes of diabetic ketoacidosis (DKA) were reported in either the CGM or SMBG group over 6 months.

Observational studies

In patients initially randomized to FCGM who subsequently participated in the 6 month open-label phase of the REPLACE trial, there were no episodes of DKA reported.[59]

Quality of Life

Randomized controlled trials

Three trials reported on quality of life, all using different measures (see Appendix I for details).[17,147,154] No differences were found between CGM and SMBG in any of the quality of life measures assessed in one trial (EQ-5D, WHO-5, Diabetes Distress Scale, Hypoglycemia Fear Survey – worry subscale, and Hypoglycemia Confidence Scale).[17] Satisfaction with the use of CGM was high in this trial (mean score 4.3 on the CGM Satisfaction Scale, range 1-5 [higher score = greater satisfaction]) and most patients indicated that the perceived benefits of CGM were high and perceived hassles low; however, satisfaction was not measured in the SMBG group. A second trial measured emotional well-being using the Problem Areas in Diabetes (PAID) questionnaire and found no differences between the CGM and SMBG groups at 3 or 12 months. [154] A follow-up publication to one of the trials[147] that compared CGM with SMBG reported via the internet reported patient satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Of the original 57 patients randomized only 32 (15 in the CGM and 17 in the SMBG group) provided DTSQ data at 6 months. The mean overall satisfaction score, as well as scores on the individual satisfaction components, were all significantly lower (i.e., worse) for the CGM versus the internet SMBG group (p-values ranged from <0.0001 to 0.015); there was no difference between the groups in perceived frequency of unacceptably low or high blood sugars (Appendix I).

One RCT (REPLACE) evaluating FCGM[58] reported significantly higher satisfaction among FCGM compared with SMBG patients at 6 months as assessed by the mean total treatment satisfaction score of the DTSQ (13.1 ± SE 0.50 vs. 9.0 ± SE 0.72, respectively; p<0.0001) and the mean satisfaction with treatment subscore of the Diabetes Quality of Life Questionnaire (DQoL) (-0.2 ± SE 0.04 vs. 0.0 ± SE 0.06, respectively; p=0.026). There were no difference between groups on any other aspects of the DTSQ (perceived frequency of hypo- or hyperglycemia) or the DQoL (total score, social and diabetes worry subscores, or impact of treatment subscore).

4.2.3. Diabetes Mellitus During Pregnancy

The general findings for DM during pregnancy for the primary clinical and intermediate outcomes are briefly summarized below by type of diabetes (pre-existing type 1, pre-existing type 2). Women with gestational diabetes are considered separately in a separate section below. Detailed findings (including results for secondary outcomes) are then presented. For each outcome the number of trials noted reflects those for which data were available for that outcome for a given time frame. Not all trials reported all outcomes at each time frame of interest. No trials using newer CGM devices were identified in this population. All trials were considered to be moderately low risk of bias (Appendix E). For type 1 diabetes, the overall strength of evidence for most efficacy outcomes was considered low across interventions and comparators; all evidence was considered insufficient for type 2 diabetes. In general, if effect estimates tended to favor one treatment but failed to reach statistical significance with confidence interval crossing the null value of zero or one (perhaps due to sample size), the results are interpreted as showing no clear difference between treatments. If effect estimates are very close to zero and not statistically significant, results are interpreted as no difference between groups.

Summary of results

Pre-existing T1DM in pregnancy

Primary clinical and intermediate outcomes

- Statistically significant and clinically important differences in frequencies of caesarean section (2 trials, SOE Moderate) and newborn admission to neonatal intensive care units (1 trial, SOE Low) were found.
- No statistically significant differences were seen for the following outcomes. In some instances studies may have lacked sufficient statistical power
    - Moderated evidence (2 RCTs): Gestational age; Birthweight; Miscarriage; Preterm Delivery; Preeclampsia
    - Low SOE (1 or 2 RCTs depending on outcome): Large for gestational age; Episodes of severe neonatal and severe maternal hypoglycemia; Hypoglycemia (neonatal, maternal); Still birth; Birth trauma; and HbA1c% measures (success, ≤6.5%; mean change from baseline)
    - Insufficient evidence (1 or 2 RCTs depending on outcome): (1 or 2 RCTs depending on outcome): Major congenital anomalies; Time spent in hypoglycemia (≤70 or <63 mg/dl range)

Other outcomes (strength of evidence not assessed, see section below and appendix for details)

- Quality of life measures
- Satisfaction

Pre-existing T2DM in pregnancy

Primary clinical and intermediate outcomes
There is insufficient evidence from one very small trial to draw firm conclusions for any outcome. Small sample size likely contributed to finding no differences between CGM and SMBG for any outcome (SOE Insufficient).

4.2.3.1. Preexisting T1DM during pregnancy

Studies included (RCTs)

We identified two parallel arm trials that evaluated CGM in pregnant women with T1DM that met inclusion criteria.[48,138] One trial, Secher et al 2013,[138] also included women with T2DM who were pregnant; results for the T2DM patients are summarized separately in section 4.2.3.2. Between the two trials, sample sizes ranged from 123 to 215 women and both trials randomized patients to receive either CGM at set intervals throughout pregnancy or to routine care using SMBG. The average age was 31.5 in both trials; the mean duration of diabetes was 11 and 16.5 years. Race and ethnicity was only reported in Feig et al. and 85.6% of participants were of European origin. Pre-gestational BMI among study participants ranged of 24.9 to 25.7 kg/m^2. Women entered the trials at gestational ages ranging between 8 and 10 weeks. Baseline HbA1c values in Secher 2013 were 6.6% and 6.8% for CGM and control groups,[138] respectively, and 7.4% across all participants in Feig et al.[48] (Table 40).

Across trials, between 22% and 46% of women were on insulin pump therapy for insulin delivery. Study protocol for intervention groups were similar in both trials: participants received CGM at set intervals with study visits occurring at predetermined points throughout the duration of pregnancy. In both trials the intervention groups were asked to perform SMBG eight times per day during these same periods. Throughout pregnancy, therapeutic adjustments were made using CGM and SMBG data. Attrition in Secher et al. was low: both groups experienced a 3% attrition rate, losing three and two participants in either group due to miscarriages. Both trials were considered to be moderately low risk of bias, with the main methodological shortcoming a lack of assessor blinding. Study supplies and materials for the trials were provided by Medtronic.

The trial by Feig et al.[48] in women with preexisting T1DM who were already pregnant was conducted alongside a concurrent trial of women with T1DM who were planning to become pregnant, of whom a small subset did become pregnant and gave birth. The “planning pregnancy” trial population did not meet our inclusion criteria and is not formally included; briefly, the authors found no statistically significant difference between the CGM and SMBG groups in any outcomes measured in this population (i.e., HbA1c%, daytime and nighttime glycemic outcomes, episodes of severe hypoglycemia, e.g., diabetic ketoacidosis; the subset of these women who ended up giving birth was too small to allow for meaningful statistical comparisons). Additional data on this concurrent trial and subpopulation can be found in Appendix Table F8.

Studies included (Observational)

We also identified three observational studies meeting our inclusion criteria that evaluated CGM in pregnant women with Type 1 DM,[34,52,139] including one[34] which was a follow-up to an RCT detailed above. The sample sizes ranged from 28 to 86 participants. The mean ages of participants ranged from 30 to 32 in two studies, and was not reported by one study.[139] Duration of diabetes was reported by all studies, and ranged from 14 to 17 years. Median pre-pregnancy BMI reported by two studies[34,139] was 25 kg/m^2 whereas the third study reported a mean of 24 kg/m^2.[52] The three studies were rated as having high,[139] moderately high,[52] and moderately low risk of bias.[34] The main methodological shortcomings, besides a lack of independent blind assessment, included unclear attrition in Secher 2014 and inadequate control for potential confounders in Fresa 2013.

Table 40. Summary of Patient Characteristics for Pregnant Women with T1DM or T2DM

	Feig 2017, Secher 2013 (# of trial reporting/total)[48,138]
Characteristics	
Females, %	100% (2/2)
Age, years; mean	31.5 (2/2)
Non-hispanic white race, %	85.6%(1/2)
Total BMI, mean	25-25.7(2/2)
DM duration, years; mean	11-16.5 (2/2)
HbA1c%, mean	6.7-7.4 (2/2)
Insulin dose, units/kg/day; median	NR (2/2)
Severe hypoglycemia within 12 mos (%)	9.3% (1/2)
Type 1, no (%)	(80% *)
Females, %	100% (2/2)

BMI: body mass index; NR: not reported; SD: standard deviation; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

*Separate baseline data for T1 and T2 patients not available for Secher 2013.

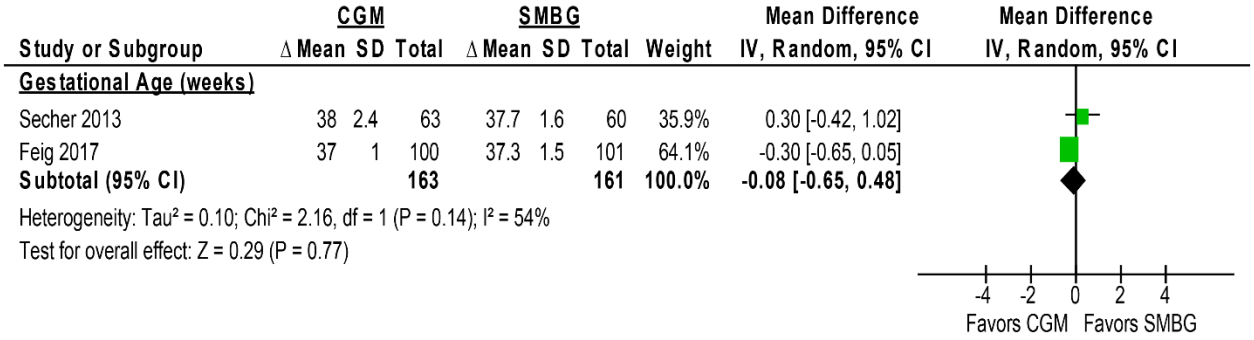
Primary Clinical Outcomes

Randomized controlled trials

Gestational age, birthweight, and large for gestational age

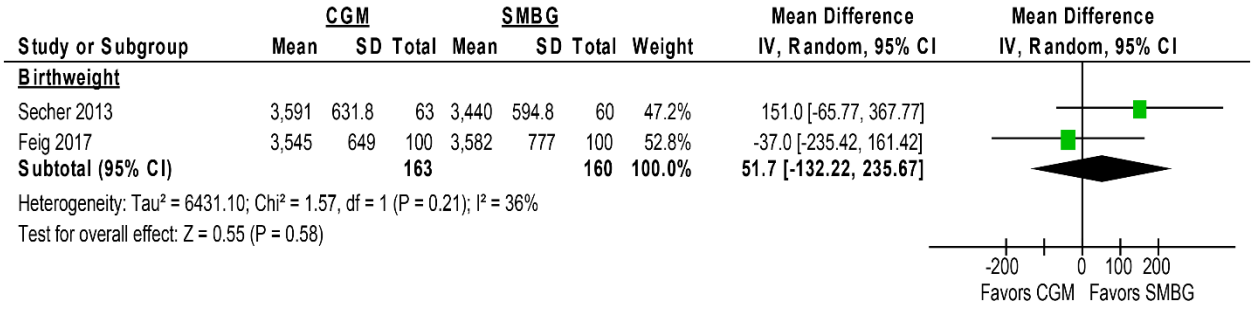
Across two RCTs,[48,138] there was no difference between the CGM and SMBG groups in gestational age at birth (pooled mean difference -0.08 weeks, 95% CI -0.65 to 0.48, I^2=54%), birthweight (pooled mean difference 51.7 grams, 95% CI -132.2 to 235.7, I^2=36%) or the proportion of infants born large for gestational age (pooled risk difference -2%, 95% CI -30% to 26% I^2=85%), Figures 39-41. Women were follow-up for 34 to 36 weeks' gestation across the trials. Substantial heterogeneity was noted for the latter outcome as the point estimates for the individual trials showed conflicting results.

Figure 39. CMG vs. SMBG in RCTs in women with pre-existing T1DM during pregnancy: Gestational age (weeks)



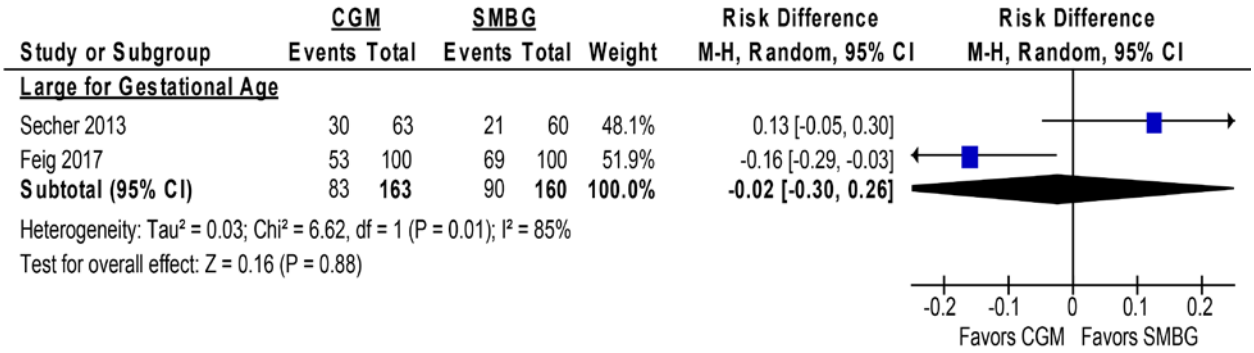
CI: confidence; CGM: continuous glucose monitoring; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus.

Figure 40. CMG vs. SMBG in RCTs in women with pre-existing T1DM during pregnancy: Birthweight (grams)



CI: confidence; CGM: continuous glucose monitoring; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus.

Figure 41. CMG vs. SMBG in RCTs in women with pre-existing T1DM during pregnancy: Large for gestational age



CI: confidence; CGM: continuous glucose monitoring; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus.

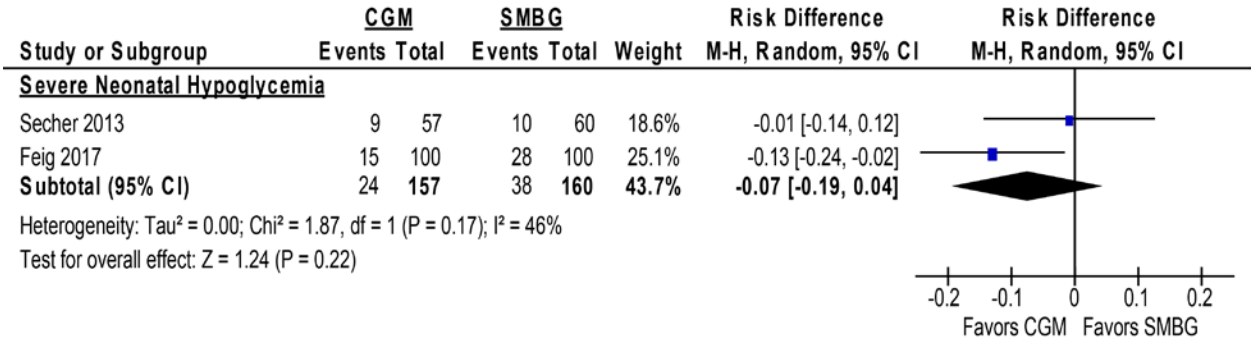
Neonatal hypoglycemia (<45 mg/dl)

There was no difference between groups in the frequency of neonatal hypoglycemia (2-hour plasma glucose <45 mg/dl) in one trial: CGM 37% versus SMBG 45%; risk difference -8.2%, 95% CI -25.9% to 9.6%.[138]

Severe neonatal hypoglycemia

There was no clear difference between CGM versus SMBG through 34 to 36 weeks' gestation in the frequency of severe neonatal hypoglycemic episodes, defined as 2-hour plasma glucose <45 mg/dl and/or requiring IV glucose infusion, according to the pooled estimate across two trials (pooled risk difference -7%, 95% CI -19% to 4%, I^2=46%), Figure 42.[48,138] Individually, one trial showed a significant benefit for CGM (risk difference -13%, 95% CI -24% to -2%; 34 weeks' gestation)[48] while the other trial showed no significant difference between groups through 36 weeks' gestation (risk difference -1%).[138] The trials were likely underpowered to detect such events.

Figure 42. CMG vs. SMBG in RCTs in women with pre-existing T1DM during pregnancy: Episodes of severe neonatal hypoglycemia



CI: confidence; CGM: continuous glucose monitoring; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus.

Major anomalies

In one trial,[48] congenital anomalies occurred in two (1.9%) and three (2.8%) infants in the CGM and SMBG groups, respectively, and consisted of aortic stenosis and hypospadias grade 1 in the CGM group and hypoplastic right heart syndrome (termination of pregnancy), aberrant right subclavian artery, and bilateral hydronephrosis in the SMBG group. In the second trial, two infants (1.6%, N=123) had major congenital malformations which included one ventricular septal defect combined with coarctation of the aorta and one congenitally corrected transposition of the great arteries.[138] The authors did not report to which group these women were randomized.

Birth trauma

In the CGM group, there were two cases (2%) of trauma to the infant during birth, one shoulder dystocia and one unspecified birth injury, as reported by one trial[48]; no instances of trauma during birth were reported in the SMBG group. Women were followed up to 34 weeks' gestation.

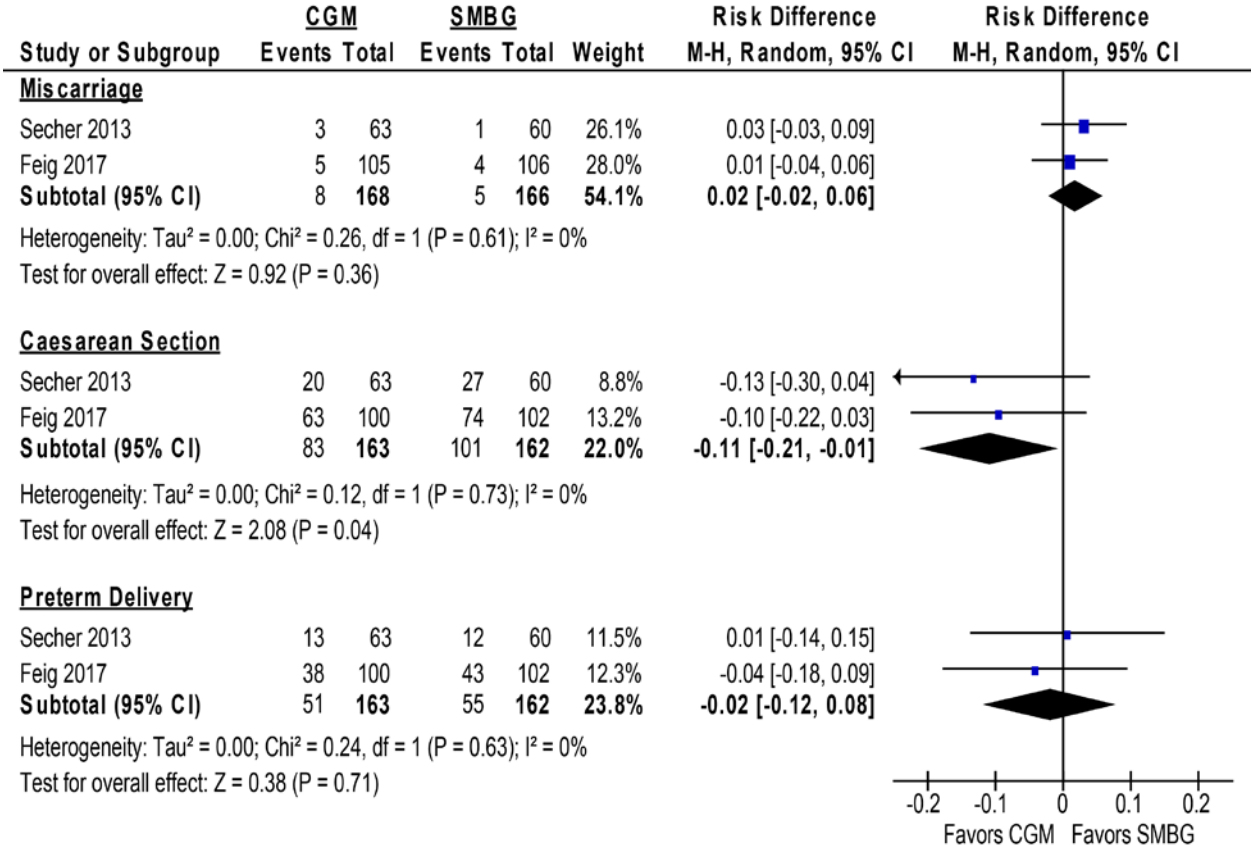
Admission to neonatal intensive care unit (NICU)

In one trial with follow-up up to 34 weeks' gestation,[48] significantly fewer infants born to mothers in the CGM versus SMBG group required high-level neonatal care (NICU) lasting greater than 24 hours: 27.0% vs. 43.0%, risk difference -11%, 95% CI -21% to -1%.

Delivery outcomes (miscarriage, caesarean section, pre-term delivery, still birth)

Across two RCTs,[48,138] significantly fewer caesarean sections were required for women using CGM (50.9%) versus SMBG (62.3%) through 34 to 36 weeks' gestation, pooled risk difference -11%, 95% CI -21% to -1%, I^2=0% (Figure 43). No significant differences were seen in the frequency of miscarriage or pre-term delivery across these two trials (Figure 43) or still birth as reported by one of these trials (0% vs. 0.9%; risk difference -0.9%. 95% CI -2.8% to 0.9%).[48]

Figure 43. CMG vs. SMBG in RCTs in women with pre-existing T1DM during pregnancy: Miscarriage, caesarean section, and preterm delivery.

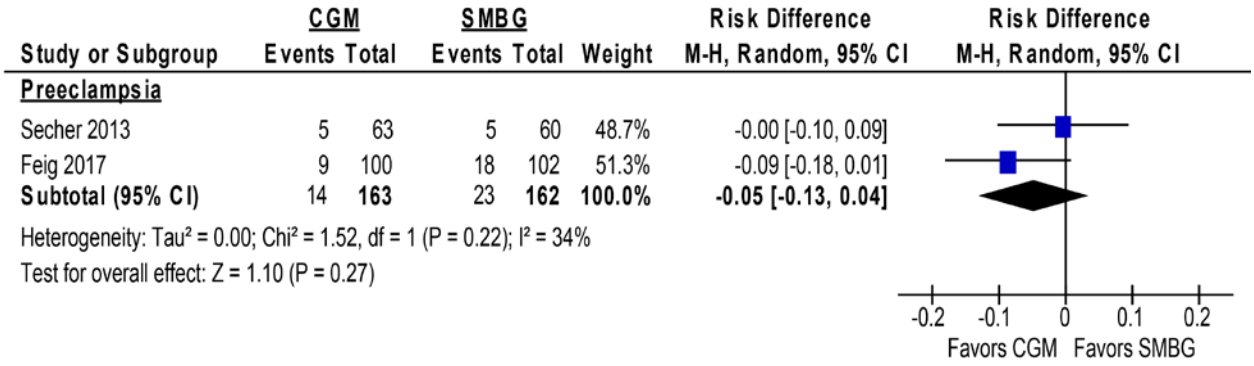


CI: confidence; CGM: continuous glucose monitoring; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus.

Preeclampsia

Across two RCTs,[48,138] there was no difference between the CGM and SMBG groups in the mother's risk of preeclampsia over 34 to 36 gestational weeks (pooled risk difference 5%, 95% CI -13% to 4%, I^2=34%), Figure 44.

Figure 44. CMG vs. SMBG in RCTs in women with pre-existing T1DM during pregnancy: Preeclampsia



CI: confidence; CGM: continuous glucose monitoring; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus.

Observational studies

Two retrospective observational studies,[34,52] one of which was a sub-analysis of the included RCT,[34] compared the use of CGM with SMBG alone specifically during labor and delivery in women with type 1 diabetes. The mean age of the women was similar across the studies (30-31 years) as was the duration of diabetes (15-16 years) and in all instances the woman had self-selected the use the CGM device. Consistent with results from the one included RCT, both studies found no statistical difference between the groups in any fetal outcome assessed (Table 41). As with the RCT, small sample size may likely play a factor.

Table 41. Fetal outcomes in retrospective cohort studies comparing CGM versus SMBG during labor and delivery in women with pre-existing type 1 diabetes.

	Cordua 2013 (subanalysis of Secher 2013) Retrospective cohort, *Moderately Low*			Fresa 2013 Retrospective cohort, *Moderately High*		
Outcome	**CGM (n=27)**	**SMBG (n=59)**		**CGM (n=18)**	**SMBG (n=47)**	
	median (range)	*median (range)*	*p-value*	*mean (SD)*	*mean (SD)*	*p-value*
Gestational age (wks.)	38 (30-40)	38 (33-39)	p=0.96	37 (2.0)	38 (1.1)	p=ns
Birth weight (g)	3,750 (1,829-4,322)	3,440 (2,045-4,424)	p=0.19	3,664 (513)	3,518 (698)	p=ns
Birth weight z-score	1.33 (-0.66 to 3.78)	0.66 (-1.06 to 3.45)	p=0.10	NR	NR	NR
	% (n)	*% (n)*	*RR (95% CI)*	*% (n)*	*% (n)*	*RR (95% CI)*

Large for gestational age (≥90th percentile)	56% (15)	36% (21)	1.57 (0.96, 2.53)	44% (8)	43% (20)	1.04 (0.57, 1.93)
Neonatal hypoglycemia	37% (10)	46% (27)	0.81 (0.46, 1.42)	6% (1)*	21% (10)*	0.26 (0.04, 1.90)
Severe neonatal hypoglycemia	11% (3)	17% (10)	0.66 (0.20, 2.19)	NR*	NR*	NR
Caesarean section	26% (7)	46% (27)	0.57 (0.28, 1.1)	83% (15)†	87% (41)†	0.96 (0.76, 1.21)
Pre-term delivery (<37 gestational wks.)	19% (5)	20% (12)	0.91 (0.36, 2.33)	17% (3)	28% (13)	0.60 (0.19, 1.87)
Respiratory disorders	NR	NR	NR	11% (2)‡	15% (7)‡	0.75 (0.17, 3.26)
Postnatal asphyxia (Apgar <5 at 5 mins.)	NR	NR	NR	0% (0)	0% (0)	IC
Neonatal ICU admission	NR	NR	NR	6% (1)	15% (7)	0.37 (0.05, 2.82)

CGM: real-time continuous glucose monitoring; g: grams; IC: incalculable; ICU: intensive care unit; ns: not statistically significant; RR: risk rato; SD: standard deviation; SMBG: self-monitoring of blood glucose; wks.: weeks
*All cases of neonatal hypoglycemia occurred in preterm deliveries; 9 cases were corrected within 3 hours of birth while two extended to 12 hours and required correction with IV glucose (unclear if these 2 would be considered "severe" and outcome not reported by group).
†Of the 56 caesarean sections, 16 (29%) were performed as emergency procedures (not reported by group).
‡Included 2 severe episodes requiring oxygen in the first 24 hours (not reported by group).

Primary Intermediate Outcomes

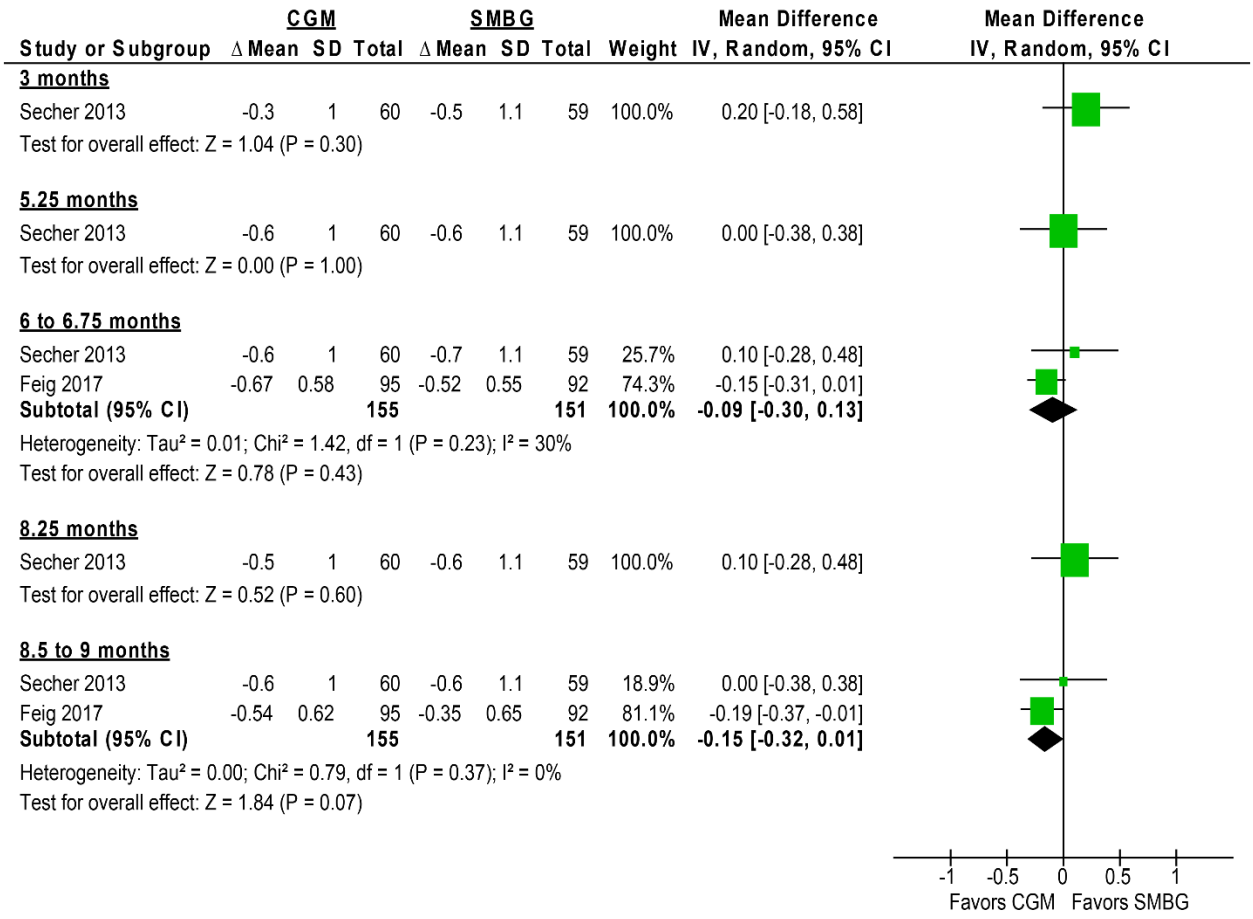
Randomized controlled trials

HbA1c %

Achieving HbA1c % target (<6.5%): There was no clear difference between the CGM and SMBG groups in the proportion of women achieving HbA1c <6.5% at 34 weeks' gestation: 66% vs. 52%, respectively; risk difference 14%, 95% CI 0.2% to 28%; p=0.060 after controlling for baseline values and mode of insulin delivery.

Change from baseline in mean HbA1c%: Across all timepoints measured up to 9 months, no statistical differences were seen between the CGM and SMBG groups in reduction from baseline in mean HbA1c % as reported by two trials (Figure 45),[48,138] though the pooled estimate at 8.5 to 9 months tended to favor CGM.

Figure 45. CMG vs. SMBG in RCTs in women with pre-existing T1DM during pregnancy: Change from baseline in mean HbA1c%



CI: confidence; CGM: continuous glucose monitoring; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus.

Maternal hypoglycemia (<63 mg/dl, <70 md/dl)

One trial reported episodes of maternal hypoglycemia defined as CGM levels <63 mg/dl for at least 20 minutes (distinct events counted only if separated by ≥30 minutes) with identical results seen for both groups through 34 weeks' gestation (median 0.5 episodes, IQR 0.3 to 0.8; p=0.73).[48] This same trial also found no difference between the CGM and SMBG groups in the percent of monitoring time spent in hypoglycemia range <63 mg/dl (median 3%, IQR 1% to 6% vs. median 4%, IQR 2% to 8%, respectively, p=0.10). Similarly, the second trial found no difference between women randomized to CGM versus SMBG in the percentage of SMBG values in hypoglycemic range <70 mg/dl (median 14% [range 0%-25%] for both groups; p=0.96) up to 36 weeks' gestation.[138] The authors also report that the women experienced a median of 4 (range 0-14) "mild" hypoglycemic events per week, with no difference between the arms (data not provided), but do not report events separately for type 1 and type 2 diabetes.

Severe maternal hypoglycemia

Both trials reported the frequency of severe maternal hypoglycemia, defined as an episode requiring third party assistance, with no differences seen between groups. In one trial,[48] a similar proportion of women in both the CGM and SMBG group experienced at least one severe hypoglycemic event through 34 weeks' gestation (10.7% [18 events] vs. 11.5% [21 events], risk difference 1%, 95% CI -9% to 8%). The second trial reported that 19 (16%) women experienced 59 severe hypoglycemic events over 36 gestational weeks, with no difference between the arms (data not provided).[138] In this same trial, the authors report that women who had used CGM per protocol (≥60% of the time) had a lower frequency of severe hypoglycemia compared with the SMBG group, 11% (4/38) vs. 19% (11/59), but the difference was not statistically significant (RD -8.1%, 95% CI -22.1% to 5.8%; RR 0.56, 95% CI 0.19 to 1.64).[138] No comparison was made between those in the CGM group who used the device ≥60% versus <60% of the time. The trial was likely underpowered to detect such events.

Observational studies

Three retrospective observational studies,[34,52,139] one of which was a sub-analysis of the included RCT,[34] compared the use of CGM with SMBG alone in pregnant women with type 1 diabetes. Two of these studies specifically evaluated women during labor and delivery[34,52]; the third included women with a recent history of severe hypoglycemia. The duration of diabetes was similar across the studies (14-16 years) and in all instances the woman had self-selected the use the CGM device.

One of the studies (N=65) evaluating women during labor and delivery reported clinically and significantly lower mean HbA1c levels in the CGM group compared with the SMBG group (5.2% ± 0.4% vs. 6.2% ± 1.7%; MD -1.0, 95% CI -1.8 to -0.2); corresponding changes from baseline were -1.1% versus -0.5%, respectively.[52] This trial also noted that none of the women experienced severe hypoglycemia (< 50 mg/dL) during delivery or needed to be switched to intravenous protocol.

The second trial (RCT subanalysis, n=86) conducted during labor and delivery, however, found no difference between groups in median HbA1c at 36 weeks (CGM 6.0, range 5.1-6.9 vs. SMBG 6.2, range 4.7-8.4; p=0.23); improvement from baseline was clinically meaningful in both groups (median -0.6% for both). [34] Of note, the trial that found statistically significant differences in HbA1c between the groups was concurrently evaluating a specific protocol for CSII use (with and without CGM) involving three different insulin basal rates according to blood glucose level; it is unclear how comparable these results may be to other circumstances.

In the third, small study (N=26),[139] eight of the 10 women using CGM during pregnancy had experienced 34 (range 1-11) severe hypoglycemic events in the year before pregnancy compared with 26 events (range 1-5) in 14 of 16 SMBG subjects; corresponding incidence rates were 2.8 versus 1.6 events per patient-year, respectively (p=0.01). From initiation of CGM until delivery, only two women in the CGM group experienced one severe hypoglycemic event each compared with one woman in the control group (0.3 vs. 0.1 events per patient-years, respectively, p=ns). Though the difference between groups in the

incidence of severe hypoglycemic events was not statistically different over the course of the study, the intervention group did experience a significantly fewer new events after initiation of CGM (p=0.0002 compared with baseline, 0.3 vs. 2.8 events per person-year).

Secondary Intermediate Outcomes

Randomized controlled trials

Hyperglycemia

The percentage of glucose values throughout pregnancy in the hyperglycemic range >144 mg/dl was reported in one trial,[138] with no difference between groups (CGM: median 28%, range 4%-44% vs. SMBG: median 28%, 4%-48%; p=0.70). The second trial found no difference between the CGM and SMBG groups in the percent of monitoring time spent in hyperglycemia range >143 mg/dl (median 3%, IQR 1% to 6% vs. median 4%, IQR 2% to 8%, respectively, p=0.10).

Health-related quality of life

No differences were found between the CGM and SMBG groups on any of the patient-reported measures assessed in one trial[48]: Blood Glucose Monitoring System Rating Questionnaire (BGMSRQ), Problem Areas in Diabetes (PAID), ShortForm-12 questionnaire, Hypoglycaemia Fear Survey (HFS II), and the CGM Satisfaction Scale (CGM-SAT) (see Appendix I for details). Mean satisfaction scores on the CGM-SAT indicated overall favorable ratings (mean 3.66 to 3.78 on a 4-point scale).

4.2.3.2. Preexisting T2DM during pregnancy

Summary of results

T2DM in pregnancy

Primary clinical outcomes

- There were no statistically significant differences seen between CGM and SMBG for the following fetal outcomes measured through 33 to 36 gestational weeks in one small trial: gestational age, birth weight, large for gestational age, neonatal hypoglycemia, miscarriage, and ceasarean section rate (SOE Low for all). One case of perinatal mortality due to severe shoulder dystocia was reported but the authors did not indicate to which group the woman was randomized (SOE Insufficient).

Primary intermediate outcomes:
HbA1C %

- There were no differences between the CGM and SMBG groups in the median reduction from baseline in HbA1c % across 8 to 36 gestational weeks in one small trial (SOE Low).

Hypoglycemia

- **Severe hypoglycemia (requiring third party intervention)**: There was no difference between CGM and SMBG with regard to the proportion of patients experiencing an episode of severe hypoglycemia through 33 to 36 gestational weeks in one small trial (SOE Insufficient). Studies were likely underpowered to detect differences.
- **Hypoglycemia (<70 mg/dL):** There was no difference between CGM and SMBG in the average percentage of glucose readings in the <70 mg/dl range throughout pregnancy in one small trial (SOE Insufficient).

Studies included

One parallel arm trial met our inclusion criteria for CGM in pregnant women with preexisting T2DM.[138] The trial also included pregnant women with T1DM and the data for this population can be found in the previous section. Out of a total population of 154 women, 31 patients had T2DM. Women were randomized to receive either CGM at set intervals during pregnancy or to continue with routine care using SMBG. Demographics were not provided separately for the type 2 population, but the median age for the total population was 32 years (range, 19 to 43), the median duration of diabetes was between 11 years (range 1 to 38 years), median pregestational BMI was 25 kg/m^2 (range, 18 to 53) and median baseline HbA1c values were between 6.7% (range, 5.3% to 10.7%). In the T2DM population, 97% of women received insulin pump therapy for insulin delivery.

During the trial, the intervention groups were asked to perform SMBG eight times per day. Throughout pregnancy, therapeutic adjustments were made using both CGM and SMBG data. The trial was considered moderately low risk of bias with the main methodological concern of a lack of independent assessment. The trial supplies and materials were provided by Medtronic.

Primary Clinical Outcomes

There were no statistical differences between the CGM and the SMBG groups in any of the primary clinical outcomes assessed in one trial (Table 42)[138]; the small sample size (N=31) was likely a factor in these findings.

Table 42. CGM versus SMBG in women with pre-existing T2DM during pregnancy: Primary clinical outcomes in the trial by Secher 2013 et al.

Author year *ROB*	Outcome	CGM % (n/N)	SMBG % (n/N)	RD (95% CI)
Secher 2013 *Moderately Low* F/U up to 36 weeks' gestation	**Caesarean section**	50% (8/16)	40% (6/15)	10% (-25% to 45%)
	Miscarriage	0% (0/16)	7% (1/15)	-7% (-19% to 6%)
	Preterm delivery	19% (3/16)	0% (0/15)	NC; p=0.23
	Preeclampsia	13% (2/16)	7% (1/15)	6% (-15% to 26%)
	Large for gestational age	25% (4/16)	27% (4/15)	-2% (-33% to 29%)
	Neonatal hypoglycemia (2-hr. plasma glucose <45 mg/dl)	31% (4/13)	14% (2/15)	17% (-13% to 48%)
	Severe neonatal hypoglycemia (2-hr. plasma glucose <45 mg/dl treated with IV glucose)	0% (0/13)	0% (0/15)	NC
	Outcome	**CGM (n=16) Median (IQR)**	**SMBG (n=15) Median (IQR)**	**p-value**
	Gestational age (weeks)	37 (29-40)	38 (37-40)	0.17
	Birth weight (grams)	3,371 (1,070-4,260)	3,343 (2,773-3,818)	0.70
	Birth weight z-score	0.27 (-2.32 to 3.18)	0.22 (-1.13 to 2.19)	0.65

CGM: continuous glucose monitoring; CI: confidence interval; F/U: follow-up; HbA1c: hemoglobin A1c; RD: risk difference; ROB: risk of bias; SMBG: self-monitoring of blood glucose; T2DM: type 2 diabetes mellitus.

Perinatal mortality due to birth trauma

There was one case of perinatal mortality shortly after delivery in an infant of a women with type 2 diabetes (3.2%, N=31) due to severe shoulder dystocia.[138] The authors did not report to which group the woman was randomized.

Primary Intermediate Outcomes

Change from baseline in mean HbA1c:

Glycemic control during pregnancy was reported in 30 (out of 31) women with with live births. Both groups showed improvement compared with baseline (gestational week 8) in HbA1c levels at all timepoints but there were no significant differences between groups. [138] (Table 43).

Table 43. Median HbA1c % levels throughout pregnancy in women with pre-existing type 2 diabetes in Secher 2013 et al.

Gestational week	CGM (n=16) median (range)	SMBG (n=14) median (range)	Effect Size	p-value*
8 weeks	6.4 (5.3-8.1)	6.5 (5.3-9.0)	NR	0.56
12 weeks	6.2 (5.6-7.8)	6.2 (5.1-7.7)	NR	0.90
21 weeks	5.7 (5.2-6.9)†	5.6 (4.6-6.3)†	NR	0.24
27 weeks	5.8 (5.0-7.7)†	5.7 (4.8-6.6)†	NR	0.28
33 weeks	6.0 (5.1-7.0)	5.9 (5.2-6.8)†	NR	0.44
36 weeks	6.0 (5.1-6.5)	5.9 (5.2-6.7)†	NR	0.31

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; SMBG: self-monitoring blood glucose

*for between-group difference.

†clinically significant improvement compared with baseline (decrease of ≥0.5%)

Maternal hypoglycemia (≤70 mg/dl)

The percentage of SMBG values throughout pregnancy that were in the hypoglycemic range ≤70 mg/dl was similar between the CGM and the SMBG groups (median 5%, range 0%-19% vs. median 4%, 0%-15%, respectively; p=0.79).[138] The authors also report that the women experienced a median of 4 (range 0-14) "mild" hypoglycemic events per week, with no difference between the arms (data not provided), but do not report events separately for type 1 and type 2 diabetes.

Severe maternal hypoglycemia

Limited comparative data was provided for the risk of severe hypoglycemia (defined as events requiring help from another person to restore normal glucose levels). A total of 5 (17%) women with type 2 diabetes experienced 15 severe hypoglycemic events during study participation,[138] with no difference between the arms (data not provided). The trial was likely underpowered to detect such events.

Secondary Intermediate Outcomes

Hyperglycemia (≥144 mg/dl):

The frequency of mild hyperglycemia was reported as the percentage of glucose values throughout pregnancy that were 144 mg/dl or higher, with no difference seen comparing women who used CGM (median 15, range 0-31) versus SMBG (median 18, range 0-35), p=0.25.[138]

4.2.4. Gestational DM

The general findings for gestational diabetes for the primary clinical and intermediate outcomes are briefly summarized below by type of diabetes (pre-existing type 1, pre-existing type 2). Detailed findings (including results for secondary outcomes) are then presented. Only one trial, considered to be moderately low risk of bias, was identified (Appendix E). All evidence was considered insufficient for this indication. In general, if effect estimates tended to favor one treatment but failed to reach statistical significance with confidence interval crossing the null value of zero or one (perhaps due to sample size), the results are interpreted as showing no clear difference between treatments. If effect estimates are very close to zero and not statistically significant, results are interpreted as no difference between groups.

Summary of results

Primary clinical and intermediate outcomes

- There is insufficient evidence from one very small trial to draw firm conclusions for any outcome. Small sample size likely contributed to finding no differences between CGM and SMBG for any outcome (SOE Insufficient).

Primary intermediate outcomes:
HbA1C %

- There were no differences between the CGM and SMBG groups in the mean reduction from baseline in HbA1c % up to 32 to 36 gestational weeks in one trial (SOE Low).

Studies included (RCTs)

We identified one parallel trial meeting our inclusion criteria that evaluated CGM in pregnant women with gestational DM.[156] A total of 106 women were randomized to CGM (n=58) or to routine care (n=62) and were instructed to continue SMBG. Mean age for both groups was 30 years. Race and ethnicity were not reported. Among participants, 76.5% and 72.7% in the intervention and control groups, respectively, had pre-gestational BMI's falling in the "Normal Weight (<25 kg/m^2)" category. Mean OGTT (oral glucose tolerance test) HbA1c values were 5.7% and 5.8% for CGM and control group participants, respectively.

All patients enrolled were diagnosed with gestational diabetes after 24 weeks gestation. They were taught to perform SMBG and were asked to check four times per day. Participants in the CGM group were further randomized to receive CGM either during the second trimester (during weeks 24-28, n=25) or the third trimester (during weeks 28 to 36, n=30). Throughout pregnancy, therapeutic adjustments were made using SMBG data. Overall attrition was 12.1% in the CGM group and 11.3% in the control group. Methodological shortcomings included lack of blinded assessor evaluation, violation of intent-to-treat principles, and unclear concealment of group allocation. This trial was considered to be moderately high risk of bias. Funding and sponsorship was not reported for this trial.

Primary Clinical Outcomes

There were no statistical differences between the CGM and the SMBG groups in any of the primary clinical outcomes assessed in one trial (Table 44)[156]; sample size was likely a factor in these findings.

Table 44. CGM versus SMBG in women with gestational diabetes: Primary clinical outcomes in the trial by Wei 2016 et al.

Author year *ROB*	Outcome	CGM % (n/N)	SMBG % (n/N)	RD (95% CI)
Wei 2016 *Moderately Low* F/U up to 36 weeks' gestation	**Caesarean section**	60.8% (31/51)	69.1% (38/55)	-8.3% (-26.4% to 9.8%)
	Perinatal death	0% (0/51)	0% (0/55)	NC
	Macrosomia (birth weight >4000 grams)	7.8% (4/51)	12.7% (7/55)	-4.9% (-16.4% to 6.6%)
	Large for gestational age (≥90th percentile)	35.3% (18/51)	52.7% (29/55)	-17.4% (-36.0% to 1.2%)
	Extremely large for gestational age (≥97th percentile)	17.6% (9/51)	30.9% (17/55)	-13.3% (-29.3% to 2.8%)
	Neonatal hypoglycemia (<45 mg/dl)	7.8% (4/51)	12.7% (7/55)	-4.9% (-16.4% to 6.6%)
	Outcome	**CGM Mean (SD)**	**SMBG Mean (SD)**	**p-value**
	Gestational age (weeks)	37.5 (1.32)	37.4 (0.99)	0.92
	Birth weight (grams)	3275.9 (519.7)	3451.1 (514.1)	0.08
	Apgar score (5 mins. post-delivery)	9.40 (0.56)	9.49 (0.50)	0.39

CGM: continuous glucose monitoring; CI: confidence interval; F/U: follow-up; HbA1c: hemoglobin A1c; RD: risk difference; ROB: risk of bias; SMBG: self-monitoring of blood glucose; T2DM: type 2 diabetes mellitus.

Preterm delivery

This trial did not report specifically on preterm delivery but stated that no births occurred before the 35th gestational week.[156]

Primary Intermediate Outcomes

Change in mean HbA1c:

At baseline (gestational weeks 24 to 28), the mean HbA1c during a oral glucose tolerance test was 5.69% ± 0.58% in the CGM group and 5.67% ± 0.29% in the SMBG group. Both groups showed a reduction from baseline in HbA1c at 32 to 36 weeks gestation, with the CGM group showing slightly lower levels compared with the SMBG group, however the difference between groups was not statistically significant (mean difference -1.00% (95% CI -0.24% to 0.04%).[156]

Hypoglycemia (<59 mg/dl):

Limited data, and no comparative data, were provided for hypoglycemia, defined as <59 mg/dl. The only information provided by the authors came from the following statement: "An average of 568 ± 30 glucose measurements were recorded and the reported hypoglycaemic episodes occurred primarily during early morning and early evening".[156] Data was not provided. The trial was likely underpowered to detect such rare events.

4.3. Key Question 2: Harms and Complications

Number of studies retained

All included comparative studies identified were evaluated for harms and complications. A total of 24 RCTs (25 publications) of traditional CGM (both parallel arm and cross-over trials) included for efficacy reported on adverse events (16 in T1DM, 3 in T2 DM, 2 in preexisting T1DM during pregnancy, 1 in preexisting T2DM in pregnancy [this trial stratifies by T1 and T2DM and is included in the count for both], and 1 in gestational DM).[14-17,19,23,39,48,58,64,67,69,79,82,89,91,97,113,115,138,149,150,152,156,163] Two trials that evaluated flash CGM (FCMG) in patients with T1DM[23] and T2DM[58] reported adverse events which are summarized separately from studies in traditional CGM below. Three observational studies included for effectiveness also reported on safety, all in people with type 1 DM.[126,145,158] Additionally, adverse events described in the FDA Summary of Safety and Effectiveness (SSED) documents for approved CGM devices are described separately.

Safety outcomes most of interest for this report include mortality and morbidity from glucose meters or monitors (i.e., device-related), therefore harms were evaluated for only those patients using CGMs with the exception of any serious or nonserious adverse events (not necessarily related to the device) when comparative data was provided. Also, since the nature of the primary safety concerns surround use of the devices themselves (and are not a function of the disease *per se*), harms are summarized across type of diabetes. When possible, we stratified adverse events by age group (children, adults, mixed children and adult populations).

The frequency of events (i.e., the proportion of patient experiencing one or more event) are reported in the table below, as well as the absolute number of events. Of note, not all studies reported both people and events. The summaries below provide ranges across all trials that report a given outcome; any trials using newer devices are included in the overall range but are also described separately.

Details of the specific adverse events reported by each study is available in Appendix Table G. Information related to alarm frequency and device accuracy for both traditional and flash CGM (e.g., detection rate, false positive rates, false negative rates, false notification rate) can be found in Appendix Tables H7 and H8. Section 5 of the report provides details of strength of evidence determination for each outcome assessed.

Summary of results:

Data across all patient populations were considered together. Events are only reported for CGM.

Inconsistent definitions, classifications and poor reporting of adverse events make it difficult to draw meaningful conclusions. There are limited data on newer devices. Most adverse events reported are sensor-related or senor-related skin problems. Events are detailed in the full report and appendices. For traditional CGM devices, SOE is low for all outcomes. Definitions and reporting of adverse events and symptoms were poor in trials of flash CGM and evidence was considered insufficient.

- **Serious device related adverse events:** Relatively rare across nine trials of traditional CGM (0% to 7%) and included insertion site infections resulting in cellulitis and skin abscess, serious skin reactions, hospitalization for ketoacidosis (including one case caused by pump failure). Two trials with newer devices report 0%-1% of patients experiencing such events. (SOE Low) Trials for flash CGM report 1%to 3% of participants experienced serious AEs related to sensor site and skin-related problems but provide no information on severity of these. (SOE Insufficient) Sample sizes were likely too small to detect rare outcomes.
- **Adverse events leading to discontinuation:** Discontinuation due to device-related adverse events was not uncommon across 6 RCT (2% to 24%). Most patients stopped CGM use due to difficulty operating the device, frequency of alarms (bothersome), or discomfort/inconvenience. Observational studies reported discontinuation of 44%-61% for similar reasons. Two trials of newer devices report discontinuation for allergic reaction (1%) and difficulty in uploading data (4%).(SOE Low) Trials of flash CGM report frequency of discontinuation in 2% to 5% of patients related to site allergic reaction, necrosis, infection, rash, pain, erythema and itching (SOE Insufficient).
- **Non-serious device-related adverse events:** Non-serious device related adverse events are common with CGM use and are primarily comprised of skin-related problems at the sensor or insulin infusion site (e.g., erythema, inflammation, rash/allergic reaction, itchiness, mild infection). Reported frequencies in non-pregnant populations ranged from 0 to 24% across RCTs and were reported at 36% in one cohort study. (SOE Low) Trials of flash CGM report "expected sensor-insertion site symptoms" (not considered AEs by the authors) in up to 40% of subjects but do not provide information regarding the distinction between events (reported as 4% to 8%) and symptoms.
- **Technical or mechanical issues:** Technical or mechanical issues reported by three RCTS included technical problems with sensor leading to loss of all glucose readings, unspecified mechanical problems, and "device issue"(in one trial of newer technology) (SOE Low)

Device-related adverse events

Serious device-related adverse events

A total of 11 RCTs, with sample sizes ranging from 14 to 244,[19,48,64,67,69,79,82,91,97,150,152] reported serious device-related adverse events (defined in Table 45 below) over 6 to 12 months of follow-up which were rare. Details are available in Appendix H. Across any age group, the frequency ranged from 0% to 7% (1 to 3 events). Excluding the one small, cross-over trial in adults with T1DM (n=14)[150] the frequency decreased to 0% to 3% across trials. The most common serious device-related complication reported across studies was insertion site infection resulting in cellulitis or skin abscess in three T1DM trials (1%, 5/555).[19,67,82] Four of the five events were due specifically to insertion of the CGM sensor (i.e., cellulitis in two subjects in two trials each (1%, 4/409),[19,82]); one trial was in a mixed population of adults and children and the other stratified by age group (8-14 years, 15-24 years, ≥25 years). In the latter, both events occurred in children age 8-14 years. In one study (n=44),[64] one patient (2%) was admitted to the hospital for ketoacidosis due to pump failure.

The frequency of serious device-related adverse events was 0% to 1% in two trials using newer CGM devices (Dexcom G4 Platinum with 505 software and Medtronic Enlite Sensor) in adults with T1DM [91,152]; only one case of retinal detachment was reported and was classified as a serious device-related adverse event by the authors.[91]

Across the FDA SSEDs (N=42 to 247) no serious or unanticipated device-related adverse events were reported over 72 hours to 3 months (Table 47).

All of the serious/severe device related adverse events reported by the two trials evaluating FCGM (N = 241, 224) were skin-related complications such as sensor insertion site reactions, erythema, rash, pain, and itching and occurred in 1% to 3% of patients (Table 48)[23,58]; in one of these patients (1%), necrosis at the sensor insertion site was reported.[58] Adverse events were poorly reported in both trials evaluating FCGM and it is unclear how adverse events were classified as severe versus nonsevere and how these events may overlap with other device-related events and sensor insertion site symptoms reported separately by the authors.

Adverse events leading to discontinuation

Eight RCTs (N=25 to 142)[15,39,64,91,115,149,152,156] reported adverse events leading to subject withdraw from the trial, the most common of which were difficulty operating the device and/or sensor in three trials (range 3% to 8%),[15,39,115] alarms to frequent in two trials (6% in both)[15,115] and treatment discomfort or inconvenience in one small trial (20%, 2/25), Table 45 (Appendix I). Across all trials, the frequency of discontinuation due to any adverse event was 1% to 24%; in the four trials of adults only with T1DM the range was 1% to 6%.[64,91,152,156]

In the trials using newer CGM devices (Dexcom G4 Platinum with 505 software and Medtronic Enlite Sensor) in adults with T1DM, one patient (1%) discontinued due to an allergic reaction to the sensor in one trial[91] and two patients (4%) in the other trial could not upload the CGM data leading to study withdrawl.[152]

Across the two trials evaluating FCGM (N = 241, 224),[23,58] 2% to 5% of patients discontinued the studies primarily due to skin-related complications (i.e., itching at sensor insertion site, erythema, rash, pain, weeping), Table 48. Again, adverse events were poorly reported in both trials evaluating FCGM and it is unclear how these events may overlap with other serious and nonserious device-related events and sensor insertion site symptoms reported separately by the authors.

Non-serious device-related adverse events

A total of seven trials, with sample sizes ranging from 25 to 157,[48,64,91,113,149,156,163] reported the frequency of non-serious device-related adverse events, which ranged from 0% to 45% (0 to 74 events) across 3 to 8.5 months of follow-up, Table 45 (Appendix I). Skin-related problems (e.g., erythema, inflammation, itchiness, rash/allergic reaction, infection) at the sensor or insulin infusion site accounted for the vast majority of these events. Of the highest frequency of these events was reported in the trial evaluating women with preexisting T1DM during pregnancy; 46 women (45%) reported a variety of skin changes

during the study period, the most common of which was acute erythema. Excluding this trial, the frequency was 0% to 24% over 6 months.

In one trial using a newer CGM device (Dexcom G4 Platinum with 505 software), 3% of patients experienced skin-related problems, including allergic reaction to sensor, inflammation, itching, and rash at application site.[91]

Across the SSEDs, 1% to 59% of subjects experienced a non-serious device-related complication, the most common of which were erythema (1% to 28%) and rash/itching (1% to 17%) (Table 47). Patients were evaluated over periods ranging from 5 days to 3 months. The SSED for the Freestyle Navigator reported that 59% (34/58) of subjects reported an adverse event related to the sensor insertion site over 5 days of observation; however, all were transient and resolved without intervention. Procedure-related adverse events were also reported by SSEDs, the most frequent of which was IV-related (e.g., pain, discomfort, brusing) in 1% to 6% of patients (n=50 to 176).

Across the two trials evaluating FCGM (N = 241, 224),[23,58] 4% to 8% of patients experienced skin-related complications described as mild or moderate device-related adverse events (Table 48). These same studies also reported sensor insertion-site symptoms (authors labeled these as "expected, not considered adverse events") which occurred frequently across both trials (28% and 40% of patients; 143 and 215 events) and consist of skin-related complications (e.g., erythema, itching, rash, bleeding, brusing, edema, induration). Again, adverse events were poorly reported in both trials evaluating FCGM and it is unclear how adverse events were classified and how these events may overlap with other serious and nonserious device-related events.

Technical/mechanical issues

Three trials reported technical or mechanical issues with the CGM device as follows: technical problems with sensor leading to loss of all glucose readings (15%, 4/27),[89] mechanical problems related to device (not further specified) (16%, 5/31) [115] and "device issue" (1%, 1/156), [91] Table 45. Additionally, one trial evaluating women with preexisting T1DM during pregnancy[48] reported that 81% of women (83/103) encountered problems with the device, the most common of which was trouble connecting transmitter to receiver; other device-related issues included sensor stopped working early, sensor did not insert properly, sensor was uncomfortable and sensor pulled out accidentally. This same trial also reported that 78% of women (80/103) did not use the device (but are assume to have continued in the trial) for a variety of reasons including alarms too frequent, inaccurate readings, too difficult to operate, sensor errors, calibration issues, and other.

One trial using a newer CGM device (Dexcom G4 Platinum with 505 software) reported that one patient (1%) had a "device issue" but does not further specify what the problem was.[91]

Across the FDA SSEDs (N=51 to 176) no technical or mechanical issues with the devices were noted; subject were following for 1 week up to 3 months (Table 47).

Neither of the trials evaluating FCGM reported on technical or mechanical issues with the device.[23,58]

Any adverse event (serious or non-serious)

Any serious adverse event

Six RCTs (N=39 to 156)[16,17,48,64,91,138] reported the proportion of patients who had experienced any serious adverse event (not necessarily related to the device, procedure or study), Table 46. In the CGM arm, the frequency was 0% to 7% compared with 0% to 13% in the SMBG arm. In one of the cross-over trials (n=153), 3% of patients required hospitalization due to diabetes-related causes[69] over the course of 12 months (two 6 month treatment periods), with no difference between the sensor-on (CGM) or sensor-off (SMBG) phases. No serious adverse events were reported in the trial of women with T1DM and T2DM using CGM during pregnancy.[138]

In the three trials using newer CGM devices (Dexcom G4 Platinum with 505 software and Medtronic Enlite Sensor) in adults with T1DM and T2DM, the frequency of any serious adverse event ranged from 2% to 5% in the CGM arms and 0% to 2% in the SMBG arms,[16,17,91] most of which were not related to the study device or procedure (e.g., cancer, pneumonia, diarrhea, inner ear disorder, pulmonary mass, trigeminal neuralgia). One trial in patients with T2DM reported one (1%) death from myocardial infarction and two cases (3%) of hospitalization for chest pain (both fully recovered), all of which were considered to be unrelated to CGM use.[17] Of note, one cross-over trial (n=156) reported five hospitalizations due to depression in one patient (0.7%) in the SMBG arm.[91]

Across the two trials evaluating FCGM (N = 241, 224),[23,58] 4% to 11% of patients using FCGM versus 3% to 16% of patients performing SMBG experienced a serious adverse event over 6 months (Table 49). Adverse events were poorly reported in both trials evaluating FCGM and it is unclear how adverse events were classified and how these events may overlap with other serious and nonserious device-related events and sensor insertion site symptoms.

Any adverse event

Four trials (N = 30 to 156)[14,48,69,89,91] reported the proportion of patients in both treatment groups who experienced any adverse event over 1 to 6.5 months of follow-up with similar frequency between groups: range 0% to 49% (0 to 137 events) for CGM and 0% to 50% (0 to 122 events) for SMBG (Table 46). The trial in pregnant women with T1DM reported a similar, high frequency of adverse events in both groups (48% vs. 43% in the CGM and SMBG groups, respectively).[48]

One crossover trial using a newer CGM device (Dexcom G4 Platinum with 505 software) reported numerous adverse events over the study period (45% CGM, 50% SMBG), most of which were unrelated to the device, study procedure, or condition being treated.[91]

Across the two trials evaluating FCGM (N = 241, 224),[23,58] 53% to 77% of patients using FCGM versus 50% to 63% of patients performing SMBG experienced any adverse event (Table 49). Adverse events were poorly reported in both trials evaluating FCGM and it is unclear how adverse events were classified and how these events may overlap with other serious and nonserious device-related events and sensor insertion site symptoms.

Table 45. Device-related harms and complications with CGM reported in RCTs

Age group*	Studies	Range of n's	Range of follow-up	Range of % of patients with ≥1 event (range of # events)
Serious device related AE: cellulitis from insertion site infection, DKA due to pump failure, skin abscess at infusion site, diabetes related hospitalization, retinal detachment, serious device or study related AE (not further specified), serious skin reactions, hospitalization for ketoacidosis				
All ages	11 (Bergenstal 2010, Hermanides 2011, Hirsch 2008, Hommel 2014, JDRF 2008, JDRF 2009, Lind 2017, Maurus 2012, Tumminia 2015, Feig 2017, van Beers 2016)	14 to 244	6 to 12 mos.	0% to 7% (0 to 3)†
Children	2 (JDRF 2008, Maurus 2012)	74 to 165	6.5 mos.	0% to 1% (0 to 2)
Adults	5 (Hermanides 2011, Lind 2017, Tumminia 2015, Feig 2017, van Beers 2016)	14 to 156	6 to 8.5 mos.	0% to 7% (0 to 3)
Mixed	4 (Bergenstal 2010, Hirsch 2008, Hommel 2014, JDRF 2009)	66 to 244	6 to 12 mos.	0% to 3% (0 to 2)†
AE leading to discontinuation‡: alarms to frequent, device too big or too difficult to operate, too busy to use device/inconvenient, intolerant of sensor use, discomfort, skin irritations				
All ages	8 (Battelino 2011, Deiss 2006, Hermanides 2011, O'Connell 2009, Tildesley 2013, Wei 2016, Lind 2017, van Beers 2016)	25 to 142	3 to 6.5 mos.	1% to 24% (1 to 9)
Adults	4 (Hermanides 2011, Wei 2016, Lind 2017, van Beers 2016)	52 to 142	3 to 6.5 mos.	1% to 6% (1 to 5)
Mixed	4 (Battelino 2011, Deiss 2006, O'Connell 2009, Tildesley 2013)	25 to 108	3 to 6 mos.	6% to 24% (5 to 9)
Non-serious device-related AE: skin related problems at sensor site (not further specified), allergic reaction to sensor, inflammation, itching at application site, rash at application site, cyst from sensor, skin infection at sensor insertion site, redness at sensor insertion site, chronic scabbing, chronic dry skin, chronic hypo or hyperpigmentation				
All ages	7 (Hermanides 2011, Lind 2017, New 2015, Yoo 2008, Tildesley 2013, Wei 2016, Feig 2017)§	25 to 157	3 to 8.5 mos.	0% to 45%§ (0 to 74)
Adults	6 (Hermanides 2011, Lind 2017, New 2015, Yoo 2008, Feig 2017, Wei 2016)§	29 to 157	3 to 8.5 mos.	0% to 45%§ (0 to 74)
Mixed	1 (Tildesley 2013)	25	6 mos.	4% (1)
Technical/mechanical issues: all glucose readings were lost, device issue (not further specified), failure of insulin pump device, replacement of radiofrequency needed				
All ages	3 (Langeland 2012, Lind 2017, O'Connell 2009)	27 to 156	1 to 6.5 mos.	1% to 16% (1 to 5)
	1 (Feig 2017)**	103	6 to 8.5 mos.	81% (274)**
Adults	2 (Langeland 2012, Lind 2017)	27 to 156	1 to 6.5 mos.	1% to 15% (1 to 4)
Mixed	1 (O'Connell 2009)	31	3 mos.	16% (5)

AEs: adverse events; CGM: continuous glucose monitoring; mos: months; RCTs: randomized controlled trials

*Only age groups for which stratified data was available for a given adverse event are included in the table. Unlike for efficacy, few trials that included mixed populations stratified safety outcomes based on age.

†Hommel 2014 does not report number of events. See Appendix Table H1 for further details

‡See Appendix Table H1 for further details.

§The trial in women with gestational diabetes (Wei 2006) reported that there were no instances of skin infection at the sensor insertion site; however, the authors do state that mild erythema, itchiness, and inflammation at sensor insertion site occurred "often" but do not provide data.
**Authors report that 81% of patients in the CGM group encountered problems with the device, primarily related to the transmitter and the sensor/sensor insertion site. Additionally, the authors report that 78% of patients stopped using the device (and our assumed to have continued the trial) for various reasons including alarms too frequent, inaccurate readings, too difficult to operate, sensor errors, calibration issues, and other. Potential overlap between the two groups was unclear.

Table 46. Any adverse event (serious and non-serious) as reported in RCTs comparing CGM with SMBG

Age group*	Studies	Range of n's	Range of follow-up	CGM range of % of patients with ≥1 event (range of # events)	SMBG range of % of patients with ≥1 event (range of # events)
Any serious AE: ≥1 event, not necessarily related to device, procedure or study					
All ages (all adults)	6 (Hermanides 2011, Lind 2017, Secher 2013, Beck 2017[a], Beck 2017[b], Feig 2017)	83 to 215	6 to 8.25 mos.	0% to 7% (0 to 9)	0% to 13% (0 to 9)
Any AE: ≥1 event, not necessarily related to device, procedure or study					
All ages	4 (Battelino 2012/Hommel 2014, Langeland 2012, Lind 2017, Feig 2017)	30 to 215	1 mos. to 8.5 mos.	0% to 49% (0 to 137)	0% to 50% (0 to 122)
Adults	3 (Langeland 2012, Lind 2017, Feig 2017)	30 to 215	1 mos. to 8.5 mos.	0% to 49% (0 to 137)	0% to 48% (0 to 122)
Mixed	1 (Battelino 2012/Hommel 2014)	153	6 mos.	45% (80)†	50% (98)†

AEs: adverse events; CGM: continuous glucose monitoring; mos: months; RCTs: randomized controlled trials; SMBG: self-monitoring blood glucose
*Only age groups for which stratified data was available for a given adverse event are included in the table. Unlike for efficacy, few trials that included mixed populations of children and adults stratified safety outcomes based on age.
†Secher 2013 did not provide information on serious adverse events for the control group. The range of the number of events is based on the remaining four studies.

Table 47. Harms and complications reported in SSEDs of FDA approved CGM devices

Outcome Age group*	Age group	Studies	Range of n's	Range of follow-up	Range of % of patients with ≥1 event† (range of # events‡)
Serious device-related AE					
Any serious device related AE	All ages	9 (DexCom G4 original study, DexCom G4 pediatric study, DexCom G4 software 505 pediatric, DexCom STS PTL9001, MiniMed 530G G100028, MiniMed 530G G110131, Paradigm/Guardian REAL-Time, MiniMed 530G ASPIRE, MiniMed 670G run-in)	42 to 247	72 hrs. to 3 mos.	0% (0)
	Children	3 (DexCom G4 pediatric study, DexCom software 505 pediatric, Paradigm/Guardian REAL-Time)	61 to 176	6 days to 7 days	0% (0)
	Adults	3 (MiniMed ASPIRE, MiniMed 670G, MiniMed G110131)	89 to 247	6 days to 3 mos.	0% (0)
	Mixed	3 (DexCom G4 original study, DexCom STS PTL9001, MiniMed G100028)	42 to 72	72 hrs. to 7 days	0% (0)
Unanticipated device-related AE					
Any unanticipated device-related AE	All ages	8 (DexCom G4 original study, DexCom G4 pediatric study, DexCom G4 software 505 pediatric, DexCom STS PTL9001, MiniMed 530G G100028, MiniMed 530G G110131, MiniMed ASPIRE, MiniMed 670G study)	42 to 247	72 hrs. to 3.5 mos.	0% (0)
	Children	2 (DexCom G4 pediatric study, DexCom G4 software 505 pediatric)	79 to 176	7 days	0% (0)
	Adults	3 (DexCom G4 original study, DexCom STS PTL9001, MiniMed 530G G110131)	42 to 90	72 hrs. to 6 days	0% (0)
	Mixed	3 (MiniMed 530G G100028, MiniMed ASPIRE, MiniMed 670G study)	50 to 247	14 days to 3.5 mos.	0% (0)
Device-related AE					
Any device-related AE	All ages	8 (DexCom G4 original study, DexCom G4 pediatric study, DexCom G4 software 505, MiniMed 530G G100028, MiniMed 530G G110131, Paradigm/Guardian REAL-Time, Freestyle Navigator [2 outcomes], Freestyle Libre Flash)	50 to 176	5 days to 10 days	1% to 59%† (1 to 22‡)
	Children	2 (DexCom G4 pediatric study, Paradigm/Guardian REAL-Time)	61 to 176	6 days to 7 days	6% to 8% (5 to 17)
	Adults	5 (DexCom G4 original study, DexCom G4 software 505, MiniMed 530G G110131, Freestyle Navigator [2 outcomes], Freestyle Libre Flash)	50 to 90	5 days to 10 days	1% to 59%† (1 to 22‡)
	Mixed	1 (MiniMed 530G G100028)	50	NR	4% (2)
	All ages	1 (MiniMed ASPIRE)	247	3 mos.	NR

Any skin-related adverse AE	Mixed	1 (MiniMed ASPIRE)	247	3 mos.	NR
Bleeding or bruising at sensor insertion site	All ages	7 (DexCom STS PTL9000, DexCom STS PTL9001, Paradigm/Guardian REAL-Time, MiniMed 530G G100028, DexCom G4 pediatric study, DexCom G4 software 505 pediatric, Freestyle Libre Flash)	31 to 176	12 hrs. to 10 days	0% to 6% (0 to 3)
	Children	3 (DexCom G4 pediatric study, DexCom G4 software 505 pediatric, Paradigm/Guardian REAL-Time)	61 to 176	6 days to 7 days	0% to 2% (0 to 1)
	Adults	3 (DexCom STS PTL9000, DexCom STS PTL9001, Freestyle Libre Flash)	31 to 50	12 hrs. to 10 days	2% to 6% (1 to 3)
	Mixed	1 (MiniMed 530G G100028)	NR	50	2% (1)
Blisters	All ages	5 (Freestyle navigator, DexCom STS PTL9000, DexCom STS PTL9001, MiniMed 670G run-in, DexCom STS pivotal study)	31 to 91	12 hrs. to 14 days	1% to 2%† (1 to 2‡)
	Adults	4 (Freestyle navigator, DexCom STS PTL9000, DexCom STS PTL9001, DexCom STS pivotal study)	31 to 91	12 hrs. to 9 days	2%† (1 to 2‡)
	Mixed	1 (MiniMed 670G)	89	14 days	1% (1)
Edema	All ages	5 (DexCom STS PTL9000, DexCom STS PTL9001, DexCom STS pivotal study, DexCom G4 software 505 pediatric, DexCom G4 original study)	31 to 91	12 hrs. to 9 days	2% to 3%† (1 to 3)
	Children	1 (DexCom G4 software 505 pediatric)	79	7 days	3% (2)
	Adults	4 (DexCom STS PTL9000, DexCom STS PTL9001, DexCom STS pivotal study, DexCom G4 original study)	31 to 91	12 hrs. to 9 days	2% to 3%† (1 to 3)
Erythema	All ages	9 (DexCom STS PTL9000, DexCom STS PTL9001, DexCom STS pivotal study, DexCom G4 original study [2 outcomes], DexCom G4 software 505 [2 outcomes], DexCom G4 software 505 pediatric, DexCom G4 pediatric study, Freestyle Libre Flash, Freestyle navigator)	31 to 176	12 hrs. to 10 days	1% to 28%† (1 to 17‡)
	Children	2 (DexCom G4 software 505 pediatric, DexCom G4 pediatric study)	79 to 176	7 days	1% to 9% (1 to 7)
	Adults	7 (DexCom STS PTL9000, DexCom STS PTL9001, DexCom STS pivotal study, DexCom G4 original study [2 outcomes], DexCom G4 software 505 [2 outcomes], Freestyle Libre Flash, Freestyle navigator)	31 to 91	12 hrs. to 10 days	4% to 28%† (3 to 17‡)
Edema or Erythema	Children	1 (DexCom G4 pediatric [2 outcomes])	176	7 days	1% to 5% (1 to 16)
Infection	All ages	4 (DexCom G4 original study, DexCom G4 software 505, DexCom G4 pediatric, DexCom G4 software 505 pediatric)	51 to 176	7 days	0% (0)

	Children	2 (DexCom G4 original study, DexCom G4 software 505)	51 to 72	7 days	0% (0)
	Adults	2 (DexCom G4 pediatric, DexCom G4 software 505 pediatric)	79 to 176	7 days	0% (0)
Pain	All ages	3 (DexCom G4 pediatric, MiniMed 530G 110131, Paradigm/Guardian REAL-Time)	61 to 176	6 to 7 days	1% to 2% (1)
	Children	2 (DexCom G4 pediatric, Paradigm/Guardian REAL-Time)	61 to 176	6 to 7 days	1% to 2% (1)
	Adults	1 (MiniMed 530G 110131)	90	6 days	1% (1)
Rash, itching	All ages	3 (Paradigm/Guardian REAL-Time [2 outcomes], MiniMed 670G run-in, Freestyle navigator)	58 to 89	5 to 14 days	1% to 17% (1 to 10)
	Children	1 (Paradigm/Guardian REAL-Time [2 outcomes])	61	6 days	2% to 3% (1 to 2)
	Adults	1 (MiniMed 670G run-in)	89	14 days	1% (1)
	Mixed	1 (Freestyle navigator)	58	5 days	17% (10)
Technical or mechanical issues	All ages	5 (DexCom G4 original study, DexCom G4 pediatric, DexCom G4 software 505 pediatric, DexCom software 505, MiniMed 530G ASPIRE [2 outcomes])	51 to 176	7 to 3 mos.	0%† (0‡)
	Children	2 (DexCom G4 pediatric, DexCom G4 software 505 pediatric)	79 to 176	7 days	0% (0)
	Adults	2 (DexCom G4 original study, DexCom software 505)	51 to 72	7 days	0% (0)
	Mixed	1 (MiniMed 530G ASPIRE [2 outcomes])	247	3 mos.	NR
Other§	All ages	2 (MiniMed 530G pivotal study, MiniMed 670G)	50 to 123	3.5 mos.	2% to 14% (1 to 17)
	Mixed	2 (MiniMed 530G pivotal study, MiniMed 670G study)	50 to 123	3.5 mos	2% to 14% (1 to 17)
Procedure-related AE					
Any procedure-related AE	All ages	4 (DexCom G4 software 505, Freestyle Libre Flash, MiniMed 530G G100028, MiniMed 530G G110131)	50 to 90	6 to 10 days	2% to 16% (1 to 11)
	Adults	3 (DexCom G4 software 505, Freestyle Libre Flash, MiniMed 530G G110131)	50 to 90	6 to 10 days	2% to 16% (1 to 11)
	Mixed	1 (MiniMed 530G G100028)	50	NR	10% (6)
IV-related (e.g. pain, discomfort, bruising)	All ages	7 (DexCom G4 software 505 pediatric, DexCom G4 pediatric, Freestyle Libre Flash [2 outcomes], MiniMed 530G G110131, MiniMed 530G G100028, MiniMed 530G ASPIRE, MiniMed 670G study [2 outcomes])	50 to 176	6 days to 3.5 mos.	1% to 6%† (1 to 5‡)
	Children	2 (DexCom G4 software 505 pediatric, DexCom G4 pediatric)	79 to 176	7 days	1% (1)
	Adults	2 (Freestyle Libre Flash [2 outcomes], MiniMed 530G G110131)	50 to 90	6 to 10 days	6% (3 to 5)
	Mixed	3 (MiniMed 530G G100028, MiniMed 530G ASPIRE, MiniMed 670G study [2 outcomes])	50 to 247	3 to 3.5 mos.	1% to 2%† (1 to 2‡)
	All ages	5 (MiniMed 530G G110131, MiniMed 530G G100028, DexCom G4 software	50 to 123	6 days to 3.5 mos.	1% to 2% (1 to 2)

Other skin irritation or pain/discomfort		505, MiniMed 670G study, Freestyle Libre Flash)			
	Adults	3 (DexCom G4 software 505, Freestyle Libre Flash, MiniMed 530G G110131)	50 to 90	6 to 10 days	1% to 2% (1)
	Mixed	2 (MiniMed 530G G100028, MiniMed 670G study)	50 to 123	3.5 mos.	1% to 2% (1 to 2)
Other**	All ages	3 (MiniMed 530G ASPIRE, MiniMed 530G G100028 [2 outcomes], MiniMed 530G G110131)	50 to 247	6 days to 3 mos.	1% to 2%† (1 to 2‡)
	Adults	1 (MiniMed 530G G110131)	90	6 days	1% (1)
	Mixed	2 (MiniMed 530G ASPIRE, MiniMed 530G G100028 [2 outcomes])	50 to 247	3 mos.	2%† (1‡)
Any device and/or procedure-related AE					
Any device and/or procedure-related AE	All ages	6 (DexCom STS PTL9000, DexCom STS PTL9001, DexCom STS pivotal study, DexCom G4 pediatric, MiniMed 530G ASPIRE, MiniMed 530G G100028)	31 to 247	12 hrs. to 3 mos.	2% to 45%† (1 to 21‡)
	Children	1 (DexCom G4 pediatric)	176	7 days	2% (4)
	Adults	3 (DexCom STS PTL9000, DexCom STS PTL9001, DexCom STS pivotal study)	31 to 91	12 hrs. to 9 days	18 to 45% (19 to 21)
	Mixed	2 (MiniMed 530G ASPIRE, MiniMed 530G G100028)	50 to 247	3 mos.	2%† (1‡)
Any serious AE (not necessarily related to device, procedure, or study)					
Any serious AE (not necessarily related to device, procedure, or study)	All ages	3 (MiniMed 530G G100028, MiniMed 530G G110131, Freestyle navigator)	50 to 90	5 to 6 days	0% (0‡)
	Adults	2 (MiniMed 530G G110131, Freestyle navigator)	58 to 90	5 to 6 days	0% (0‡)
	Mixed	1 (MiniMed 530G G100028)	50	NR	0% (0)
Any AE (not necessarily related to device, procedure, or study)					
Any AE (not necessarily related to device, procedure, or study)	All ages	6 (DexCom G4 original study [2 outcomes], DexCom G4 software 505, DexCom G4 pediatric, DexCom G4 software 505 pediatric, MiniMed 530G G110131 [2 outcomes], MiniMed 530G G100028 [2 outcomes])	50 to 176	6 to 7 days	8% to 42%† (10 to 38‡)
	Children	2 (DexCom G4 pediatric, DexCom G4 software 505 pediatric)	79 to 176	7 days	8% to 13%† (10 to 21)
	Adults	3 (DexCom G4 original study [2 outcomes], DexCom G4 software 505, MiniMed 530G G110131 [2 outcomes])	51 to 90	6 to 7 days	14%† (13 to 38‡)
	Mixed	1 (MiniMed 530G G100028 [2 outcomes])	50	NR	36% to 42% (20 to 29)

AE: adverse event; CGM: continuous glucose monitoring; FDA: Federal Drug Administration; hrs: hours; mos: months; NR: not reported

*Only age groups for which stratified data was available for a given adverse event are included in the table.

†Not all studies reported number of events. See Appendix table H4 for further details.

‡Not all studies reported number of events. See Appendix table H4 for further details

§Includes urine ketones due to improper infusion tubing connection and device-related events leading to hyperglycemia

**Included emesis due to study procedure, headache due to study procedure, and loss of dental filling due to study procedure

Table 48. Device-related harms and complications reported in RCTs evaluating flash CGM (Libre device).

Studies	Duration of device use	N	Follow-up	% of patients with ≥1 event (total events)
AE or device associated symptom leading to discontinuation*: Itching at sensor insertion site, erythema, rash, pain, redness, weeping, other (NR)				
Bolinder 2016	6 mos	120	6 mos	5% (6)
Haak 2016	6 mos	149	6 mos	2% (3)
Device related AE, serious/severe*: Allergic reaction, infection, or necrosis at sensor site insertion, erythema, rash, pain, itching,				
Bolinder 2016	6 mos	120	6 mos	3% (6)
Haak 2016	6 mos	149	6 mos	1% (2)
Device related AE, any*: Erythema, itching, rash, reaction, necrosis, or infection at sensor insertion site; pain; oedema; redness; pustules; weeping				
Bolinder 2016	6 mos	120	6 mos	8% (13)
Haak 2016	6 mos	149	6 mos	4% (9)
Sensor insertion-site symptoms (expected, not considered AEs)*: Erythema, itching, rash, pain bleeding, bruising, oedema, induration				
Bolinder 2016	6 mos	120	6 mos	40% (215)
Haak 2016	6 mos	149	6 mos	28% (143)

AE: adverse event; CGM: continuous glucose monitoring; mos.: months; NR: not reported; RCT: randomized controlled trial.
*The distinction between "device related AEs (serious or not serious)" and "sensor insertion-site symptoms" was not clearly reported by study authors. Patients may have experienced both a device related AE and a sensor insertion-site symptom, but the study did not provide enough information to delineate.

Table 49. Any adverse event (serious or nonserious) reported in RCTs evaluating flash CGM (Libre device).

Studies	CGM, n	SMBG, n	Follow-up	CGM: % of patients with ≥1 event (total events)	SMBG: % of patients with ≥1 event (total events)
Any serious AE: ≥1 event, not necessarily related to/unclear if related to device, procedure or study*					
Bolinder 2016	120	121	6 mos	4% (5)	3% (5)
Haak 2016	149	75	6 mos	11% (NR)†	16% (NR)†
Any AE: ≥1 event, not necessarily related to/unclear if related to device, procedure or study*					
Bolinder 2016	120	121	6 mos	53% (138)	50% (138)
Haak 2016	149	75	6 mos	77% (NR)	63% (NR)

*Not described further. It is unclear to what extent these percentages and events overlap with the device-related and sensor insertion site-symptom adverse events reported separately.
†Not reported by treatment group. Authors just state that "42 serious events were experienced by 16 (11%) intervention and 12 (16%) control participants".
‡Not reported by treatment group. Authors just state that "In total, 515 serious adverse or adverse events were experienced by 114 (77%) intervention and 47 (63%) control participants".

4.4. Key Question 3: Differential Efficacy and Harms in Subpopulations

4.4.1. Number of studies retained

For this key question, RCTs that stratified on baseline patient characteristics and evaluated effect modification were sought. Subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. All RCTs included to evaluate the efficacy or safety of CGM versus comparators of interest were assessed. Information on subgroup analyses if applicable is presented for each outcome in previous sections (e.g., adherence to CGM use). To evaluate the presence of differential efficacy or safety, the potential that chance may explain differences (i.e. modification of treatment) between subgroups needs to be statistically tested via a test for interaction.

Summary of results:

- In one trial of adults with T1DM, none of the baseline factors analyzed (baseline HbA1c, age, percent of CGM time <70 mg/dl, SMBG frequency, education, hypoglycemia unawareness and fear, diabetes numeracy score, and clinical site) modified the effects of CGM for the outcome of change in HbA1c from baseline in one moderately low risk of bias trial. Sample sizes in this trial were likely inadequate to effectively test for modification. (SOE Insufficient)
- In one trial of adults with T2DM by the same authors suggests that hypoglycemic awareness or uncertainty may modify the effect of CGM on change in baseline HbA1c%. None of the other exposures appeared to modify the association with change in HbA1c%. Sample sizes in this trial were likely inadequate to effectively test for modification. (SOE Insufficient)

4.4.2. T1DM in Adults

One of the RCTs (DIAMOND trial)[16] included for efficacy that compared CGM with SMBG (both using MDI) in adults with type 1 diabetes evaluated effect modification and conducted a formal test for interaction. None of the following characteristics modified treatment effect of CGM versus SMBG for the outcome of change in HbA1c (%) from baseline to 6 months in this trial (see Appendix I for details):

- Baseline HbA1c (<8.5% vs. ≥8.5%), interaction p=0.16
- Age (25 to <45 vs. 45 to <60 vs. ≥60 years), interaction p=0.18
- Percent of CGM time <70 mg/dl (<5% vs. ≥5%), interaction p=0.10
- SMBG frequency (≤3 vs. ≥4 time per day), interaction p=0.44
- Education (<Bachelor's degree vs. ≥Bachelor's degree), interaction p=0.49
- Hypoglycemia Unawareness (reduced awareness [score ≥3] vs. aware [score ≤2]), interaction p=0.32
- Diabetes Numeracy Score (≤3 out of 5 correct vs. ≥4 out of 5 correct), interaction p=0.55

- Hypoglycemia Fear Total Score (0-13 vs. 14-77), interaction p=0.14
- Type of clinical site (Community vs. Academic), interaction p=0.07

4.4.3. T2DM in Adults

One of the RCTs (DIAMOND trial)[17] included for efficacy that compared CGM with SMBG (both using MDI) in adults with type 2 diabetes evaluated effect modification and conducted a formal test for interaction. Only baseline Hypoglycemia Unawareness Survey scores were found to modify treatment effect such that statistically greater reduction in mean HbA1c % levels from baseline to 6 months was seen in subjects with reduced awareness or uncertainty (score ≥3), compared with higher awareness (score ≤2), following CGM but not SMBG (interaction p=0.031), Table 50.

Table 50. Heterogeneity of treatment effect in adults with T2DM in the trial by Beck et al. 2017

Hypoglycemia Unawareness Survey score	Mean change (± SD) in HbA1c %, baseline to 6 months		p-value for interaction*
	CGM (n=77)	SMBG (n=75)	
Reduced awareness or uncertain (≥3)	−0.8 ± 0.7 (n=24)	−0.2 ± 1.0 (n=16)	0.031
Aware (≤2)	−0.9 (0.7) (n=53)	−0.6 ± 0.8 (n=59)	

*Obtained by including interaction term in each mixed effects model with baseline HbA1c level as a fixed effect and clinical site as a random effect.

None of the following characteristics modified treatment effect of CGM versus SMBG for the outcome of change in HbA1c (%) from baseline to 6 months in this trial (see Appendix I for details):

- Baseline HbA1c (<8.5% vs. ≥8.5%), interaction p=0.35
- Age (≤44 vs. 45 to 59 vs. ≥60 years), interaction p=0.89
- Percent of CGM time <70 mg/dl (<5% vs. ≥5%), interaction p=0.55
- SMBG frequency (≤3 vs. ≥4 time per day), interaction p=0.78
- Education (<Bachelor's degree vs. ≥Bachelor's degree), interaction p=0.64
- Diabetes Numeracy Score (≤3 out of 5 correct vs. ≥4 out of 5 correct), interaction p=0.39
- Hypoglycemia Fear Total Score (0-13 vs. 14-77), interaction p=0.72

One trial evaluating FCGM[58] stated that there was an significant interaction (p=0.0017) between age (<65 years vs. ≥65 years) and study group regarding the change from baseline to 6 months; however, authors do not provide enough data to confirm these findings.

4.5. Key Question 4: Cost effectiveness

Number of studies retained

Five cost-utility analyses (CUA) were identified that met the inclusion criteria assessing the cost effectiveness of CGM versus SMBG, four of which considered patients with type 1 diabetes [29,70,99,131] and one modeled a population of type 2 diabetes. [49] All studies focused on adult populations, each study involving T1DM patients adopted societal perspectives, attempting to incorporate both direct and indirect costs, while the study with type 2 patients assumed a healthcare perspective and focused only on direct costs. All analyses implemented some form of Markov Model to forecast long-term costs of health outcomes. The main outcome measured in all five of the studies was the incremental cost effectiveness ratio (ICER), which expresses the marginal cost of adding one quality adjusted life year (QALY) to a patient's life when using CMG compared to SMBG.

Each of the studies retained was scored using the Quality of Health Economic Studies (QHES) instrument, a standardized metric to assess the soundness of economic evaluations. Scores were fairly high and studies relatively well conducted. The average QHES score was (84.6 ±6.1). The lowest score was 75 and the highest 92. Chief among concerns were, in some instances, the sourcing of relevant model parameters, applicability to American healthcare environment due to the international nature of two [29,131] of the analyses and also industrial ties the three. [29,49,131]

Summary of Economic Studies

- Five cost-utility analyses (CUA) in adults evaluated the cost effectiveness of CGM versus SMBG, four of which were in adults with type 1 DM and one in adults with type 2 DM. Four studies were funded by industry. Only one included data based on newer devices. Assumptions regarding baseline HbA1c% and changes resulting from CGM use differed across studies. Quality of studies overall was moderately good to good (QHES scores 75 to 92). No full economic studies related to use of CGM in persons <18 years old or in pregnancy were identified.
- Adults with type 1 DM: 2 Two CUA were conducted in the U.S, one in Canada and one in Sweden. All claimed a societal perspective; however one did not provide information on indirect cost. In general, all concluded that CGM may be cost-effective.
    - Base case ICERs across studies of adults with type 1DM ranged from $43,926/ QALY to $98,679/QALY. Ranges from sensitivity analyses ranged from $42,552/QALY to over $700,000/QALY. Across studies, authors concluded that CGM may be cost-effective at a willingness to pay of $50,000 to $100,000.
    - Limitations:

  - Models assumed a long-term horizon (>30 years). RCT data for CGM use in included trials is reported for up to 12 months for older devices, 6 months for newer devices.
  - Results from modeling long term outcomes using hypothetical cohorts, as three of the studies relied solely on, are largely dependent on the assumptions used in selecting the parameters, only some of which were addressed or reported in sensitivity analysis.
  - Sensitivity analysis related to model assumptions for long-term micro and macrovascular disease is poorly presented across studies and the impact on cost-effectiveness is unclear across studies; Two studies that evaluated such complications more extensively reported greater variability in estimated cost-effectiveness. Modeling of CGM adherence and other "real-life" factors are not presented in sensitivity analyses.
- Adults with type 2 DM not taking prandial insulin: One CUA conducted in the U.S. using UK trial data from a payer perspective reported ICER of $8,898 /QALY.
  - Probabilistic cost-effectiveness analysis suggests that the likelihood of the intervention being cost-effective is 70% at the willingness-to-pay threshold of $100 000 per QALY over a lifetime time horizon based modeling of a hypothetical cohort.

Study limitations included every limited sensitivity analyses, modeling of life-time use (limited long-term data in adults with type 2 diabetes, use of older CGM devices. It is unclear if the data in models for complications from older diabetes treatment and the Framingham study reflect current care.

T1DM

Study characteristics and framework

Four CUAs evaluated the cost effectiveness of CGM versus SMBG in patients with type 1 diabetes. Two were conducted in the United States,[70,99] one in Canada,[29] and one in Sweden.[131] All foreign currencies were extracted and converted here to reflect each study's costing year's equivalent in US dollars using the official US Federal Reserve exchange rates.[22] Costing years range from 2007 to 2016. Most of the studies had similar demographics with respect to age and gender. There was a slightly higher proportion of females and three of the four studies had an average age within 3-years of 43-years-old with the exception of one study[131] which was considerably younger at 27-years-old. All models considered long term cost implications. The minimum forecast was 33 years, however, most modeled outcomes for patients' remaining lifetime.

Baseline HbAc1 ranged from 7.4% up to 8.6%. The industry funded, Canadian-based study assumed the largest difference in reduction rates of HbAc1 between CGM and SMBG. In all studies CGM was favorable. The Canadian study assumed a 0.6% greater reduction produced by CGM. At the same time, the Swedish study modeled long term complication rates under the assumption of a 0.3% greater reduction. The two American studies were similar in assuming a 0.5% greater reduction for CGM.

An important element to several of the studies was the QunitileIMS CORE Diabetes the Model (CDM). This interactive simulator was the basis for three[29,99,131] analyses investigating those with T1DM and directly implemented in two.[29,131] The study of persons with type 2 diabetes also used this model. The

authors that relied on this tool proposed that because it has been widely validated,[98] additional model building was determined unnecessary. In effect, CDM synthesizes 17 Markov-based sub models, all running simultaneously, to describe the development of diabetes-related complications over a long term forecast. Leading complications included in the model are angina, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, neuropathy, foot ulcer, amputation, renal disease, and eye disease. Each sub model incorporates baseline probabilities of risk and health transition rates derived from published sources. One such source was the DIAMOND RCT,[16] which was used by the Canadian study, while the Swedish study used the DCCT and JDRF trials. [16,107] Costs were then calculated according to the forecasted health states.

The remaining study that did not rely on the CORE Diabetes Model estimated within-trial quality-of-life (QoL) using a random effects linear model. These estimates were then combined with a lifetime analysis, which like the others, used a health state-transitioning Markov model. The possible health states were broken into modules and included retinopathy, nephropathy, neuropathy, ischemic heart, myocardial infarction, congestive heart failure, stroke.

All studies assumed a societal perspective and reported both direct and indirect costs. Key driving costs could be broken into three categories 1) intervention (sensor, test strips, training and other), 2) complication (cardiovascular, renal, hypoglycemia, eye disease, others) and 3) indirect cost (including productivity loss captured in lost wages). Cost of CGM technology reported ranged from $3,729 to $6,394.

Study characteristics, results and conclusions are summarized in Table 51.

Base Case Results

Base case results were relatively consistent across the four trial, despite varying intermediate values. The two foreign studies had the lowest lifetime projected costs. The Canadian assessment of total direct and indirect cost associated with type 1 diabetes was $440,955 and 293,621 for CGM and SMBG respectively. The Swedish study estimated the costs to be $448,832 and $405,088. Notably, this study was one with a markedly younger average age (nearly 20 years younger than the Canadian study). In comparison, the two American studies had the highest estimations and reported remaining lifetime costs for CGM to $494,135 and $659,837 with SMBG costing $470,583 and $601,070. Therefore, in all cases CGM was the costlier alternative. Across all studies the average cost difference was $68,349.

Meanwhile, the difference in quality-adjusted life years (QALYs) added by CGM ranged from 0.52 QALYs to 3.35 QALYs in favor of CGM. The corresponding cost for each QALY was lowest in the SMBG arm Swedish study at $32,961/QALY and highest in the SMBG arm of the Canadian study at $58,374/QALY.

The ICER summarized the differences in costs and effectiveness by expressing the incremental cost of using CGM versus SMBG for adding one additional full-quality year to a patient's life. The ICER of the Canadian study was the lowest at $43,926/QALY. While the American study that built its own model incorporating within-trial QoL assessments along with lifetime analysis of costs was the highest at $98,679/QALY. The remaining studies fell fairly in the middle estimating ICERs of $45,033, and $57,433/QALY.

Sensitivity Analyses

Each of the studies employed some form of sensitivity analysis. Overall, the models proved to be relatively robust to variations of their assumptions. Altering the baseline HbA1c value was a common

choice across the studies. The Swedish study, for instance, found that by varying the baseline level from 8.6% to 7.2% then to 9% caused the ICER to fluctuate between $92,759 and $53,693/QALYs respectively. One study[99] took a unique approach and varied all parameters by %15 margins. Doing so, it found the top most influential variables driving cost-effectiveness in its model were the utility value of diabetes with no complications, the annual cost of chronic heart disease (CHD), and the probability of going from diabetes with no complications to the CHD disease state. The study then proceeded to change each of these influential parameters by 50% margins. When the utility of diabetes with no complications was decreased (and increased) by 50%, the ICER over $300,000 ($30,000)/QALY. The annual cost of CHD also had a large impact on the model results, and when decreased (increased) by 50%, the ICER was $86,000 ($12,000)/QALY. Furthermore, studies found that increasing the CGM sensor use from 48 to 51 sensors/year increase the ICER by about $1,000/QALY and that varying the number of SMBG tests/day from 7.1, though 6.1, to 2.1 resulted in a decreasing trend in the ICER of $74,292, $68,183, $43,751/QALY[131] respectively.

Conclusions and Limitations

With a willingness to pay (WTP) of $50,000, the Canadian study found CGM to be a robustly cost effective intervention compared to SMBG alone. It should be noted that this study had the closest ties to industry and in fact, was funded by a CGM device manufacturer. The next lowest ICER, which also fell below the WTP threshold, was estimated by an American study. In a Monte Carlo simulation of its results it found that 48% of the ICERs were under $50,000/QALY, while 70% were under $100,000/QALY. The other American study encountered high variability and uncertainty. The confidence interval it reported for the ICER included both the possibility that CGM dominated SMBG (meaning it was more effective while be less expensive) and also the possibility that SMBG dominated CGM. Lastly, the Swedish study (also with connections to industry) concluded that CGM was a cost effective options for the population it analyzed.

Aside from involvement for industry another potential limitation of these studies is their relatability to healthcare practice in the United States; the medical systems, pricing and costs of care in the U.S. differ from those in Sweden and Canada. Results yielded by modeling long term outcomes using hypothetical cohorts, as three of the studies relied solely on, are largely dependent on the assumptions used in selecting the parameters. The one study that incorporated both within trial cost data and combined those with forecasted future cost had a significantly different cost profile than three studies that used only hypothetical cohorts. Other issues arose in studies while estimating parameters in their models. For instance, one study was forced to substitute cardiovascular complication rates from type 2 diabetes patient population. Still others had potential problems with precision when defining the utility values associated with CGM. This fact was reflected in wide confidence intervals in sensitivity analysis. In general, the subtler issues and concerns relating to approximating variables were addressed in sensitivity analysis and potential conflicting interests were clearly disclosed. QHES scores ranged from 85 to 92.

T2DM

Study characteristics and framework

Examining patients with type 2 diabetes offers a further look into the cost effectiveness dynamics of CGM and SMBG. One study[49] was identified meeting the inclusion criteria that focused on patients with T2DM. The sample population consisted of adults (avg. age= 57.8 years) who had been diagnosed with type 2 diabetes for at least 3 months and were not taking prandial insulin. The initial A1C of the group was between 7% and 12%.

The study reported the clinical effectiveness in terms of life expectancy (LE) and quality-adjusted life years. Despite being an American study, the analysis abstract many of its measurements from an older RCT[2] done in the United Kingdom from 1998. Assumed HbA1c reduction of 1.1 (±1.5) and 0.5 (±1.3) for CGM and SMBG respectively and incorporated hypoglycemia, amputation, a myocardial infarction, among others, into its analysis. For modeling it implemented, as many of the other studies did, the CORE Diabetes Model (described above).

Costing was based on 2011 US dollars. Intervention costs of both CGM and SMBG included antidiabetic oral medications, insulin, routine management such as recommended screening, exams. Complication costs included treatment of diabetes complications, cardiovascular disease complications, renal complications, treatment for depression, acute events, eye disease, and neuropathy. Notably, cost data was provided by Dexcom, a CGM device manufacturer and primary funder of the study, and additional published literature. [2,102,117,151]

It states that univariate sensitivity analysis was performed, as well as, probabilistic sensitivity analysis.

Study characteristics, results and conclusions are summarized in Table 52.

Base Case Results
CGM was found to cost $66,094 and able to achieve an increase in quality adjusted life years of 6.03 QALY. This corresponds to a cost of $10,961 for each QALY. SMBG was estimated to cost a similar amount at $65,441 and produced and additional 5.96 QALY leading to and cost per QALY of $10,980 /QALY. The ICER $8,898 /QALY.

Sensitivity Analyses
Probabilistic cost-effectiveness analysis suggests that the likelihood of the intervention being cost-effective is 70% at the willingness-to-pay threshold of $100 000 per QALY.

Conclusions and Limitations
The authors concluded that CGM offers a cost-effective alternative to populations matching that the trial specifically: short-term, intermittent use in people with type 2 diabetes.

Leading potential limitations include an admittedly small sample size of the trial that provided many of the clinical inputs for the CORE Model. Given this concern a more extensive sensitivity analysis would have been informative to evaluate the robustness of the model. Furthermore, it made its estimates considering an older CGM device that has since been update. Other studies reviewed discussed the added effectiveness of newer models. The scope of this study also falls short of the others that met the inclusion criteria in that it considered only direct cost. Altogether these concerns led to a QHES score of 75.

Table 51. Overview of formal economic studies for T1DM.

Type 1 Studies:	Chaugule 2017[29]	Huang 2010[70]	McQueen 2011[99]	Roze 2014[131]
Population	Adult only (avg. age = 46) Baseline HbA1c = 8.6% Type I Diabetes 53% Male MDI	Included two cohorts: Baseline HbA1c = 7.6 and 7.1%: for SMBG and CGM groups respectively with avg. age = 43 (25-73) 57% Female HbA1c <7.0% avg. age = 31 (8-65) Both MDI and CSII included	Adult only (avg. age 40) with Baseline HbA1c = 7.6% Type 1 Diabetes Assumed 20 yrs. since diagnosis Both MDI and CSII included	Adult only (avg. age =27) Baseline HbA1c = 8.6% 54.5% Female Assumed 13 yrs. since diagnosis CSII
Intervention(s)	CGM	CGM	CGM	CGM
Comparator(s)	SMBG	SMBG	SMBG	SMBG
Country	Canada	United States	United States	Sweden
Funding	Dexcom Inc.	JDRF Grant	Reports no funding received	Medtronic
Study design	CUA	CUA	CUA	CUA
Perspective	Canadian societal (Stated)	Societal	Societal	Swedish societal
Time horizon	50 years	Lifetime	33 years	70 years
Analytic model	CORE Diabetes Model Cohort-based Monte Carlo Incorporating Markov sub-models	Recycled predictions for Immediate outcomes Markov model extrapolated from trial based utilities	Markov Cohort Analysis constructed in decision analysis format. Holds similarities to CORE	CORE Diabetes Model Cohort-based Monte Carlo Incorporating Markov sub-models
Effectiveness outcome	QALY	QALWeeks and QALY	QALY	QALY
Effectiveness outcome components	Assumed 0.6% HbA1c greater reduction[16] Key health states/ complications: Angina pectoris, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, DM retinopathy, cataracts, hypoglycemia, DM ketoacidosis, nephropathy, neuropathy, foot ulcer/ amputation, macular edema, and depression	Assumed 0.5% HbA1c reduction of 0.53% Health states divided into modules: Retinopathy, Nephropathy, Neuropathy, Ischemic Heart, Myocardial Infarction, Congestive Heart Failure, Stroke	Assumed 0.5% HbA1c reduction[82] Key health states/ complications: Retinopathy, nephropathy, neuropathy, Coronary Heart Disease, continue with diabetes and no complications, or death. With additional sub-diseases associated with each disease state.	Assumed 0.3% HbA1c reduction[122] with greater reduction for every extra day of sensor use per week. Key health states/ complications: Angina pectoris, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, DM retinopathy, cataracts, hypoglycemia, DM ketoacidosis, nephropathy,

Type 1 Studies:	Chaugule 2017[29]	Huang 2010[70]	McQueen 2011[99]	Roze 2014[131]
				neuropathy, foot ulcer/ amputation, macular edema, and depression
Source for effectiveness data	DIAMOND RCT[16] IMS CORE Diabetes Model	JDRF Trial[82] Health Utility Index DCCT[107] Published literature[32,71,119]	Modeled after the C.D.C. Cost-Effectiveness Group analysis, CDM, relied on professional expertise, and DCCT[107] published literature[68,80,84,146] Associated utilities taken from EQ-5D catalog	IMS CORE Diabetes Model DCCT[107] Published literature[80,162]
Costing year	2016	2010	2007	2011
Currency	1 USD = 1.3 CAD[22]	USD	USD	1 USD = 6.4 Swedish SEK[22]
Discounting	1.5%	3%	3%	3%
Components of cost data	Management cost, cardiac complications, renal complications, acute events, eye disease, neuro/foot ulcer/amputations Indirect costs: NR	Direct costs divided between personnel (staff time for training) and medical care costs (device and usage costs) Indirect cost, work/school performance. Hours devoted to diabetes care	Hospital inpatient visits, nursing/residential facility visits, physician's office visits, emergency department trips, hospital outpatient visits, home health care, hospice care, podiatry care, insulin, DM supplies, oral agents, retail prescriptions, other supplies, and patient time. Included indirect cost such as lost wages.	Intervention (Enlite sensor, test strips, and others), complication (Cardiovascular, renal, hypoglycemia, eye disease, others) and indirect cost (including production loss)
Cost sources	Canadian Formulary health.gov Published literature	Bureau of Labor Statistics Averaged device manufacturer retail prices Redbook Published Literature	Costs were derived from evidence published by the ADA and device manufacture retail prices.	Swedish Pharmaceutical Benefits Board Published Literature[63,107]
Sensitivity analysis	One-way sensitivity analyses discount rate, baseline HbA1c level, hypoglycemia-related disutility, HbA1c reduction conferred by CGM vs SMBG,	Isolated benefit to include only improved glucose control, HbA1c difference range, number of test strips 2 vs 10, daily cost of CGM	Conducted one-way and multivariate probabilistic analysis. Included varying all assumed parameters by 15%.The top 10 most	One-way sensitivity analysis: Increasing frequency of CGM from 48 to 51 sensors / yr. Number of SMBG test from 2.1 to 7.1

Type 1 Studies:	Chaugule 2017[29]	Huang 2010[70]	McQueen 2011[99]	Roze 2014[131]
	percentage reduction in NSHEs and SHEs, starting utility of patients in the simulation cohort, and fingersticks per day Probabilistic sensitivity analysis used to derive the acceptability curve.		influential variables then underwent additional testing and were varied by 50%.	Baseline HbAc1 level from 7.2 to 9% Rate of severe hypoglycemia Discount rates from 0 to 5% Complication costs from ±10%
QHES	86/100	85/100	92/100	86/100
Results:				
Cost / QALY of CGM	$440,955/ 8.38 = $52,620/QALY	$659,837 / 14.35 QALY= $45,982/QALY	$494,135 / 10.81 QALY= $45,710/QALY	$448,832 / 13.05QALY= $34,393/QALY
Cost / QALY of comparator(s)	$293,621/ 5.03 = $58,374/QALY	$601,070 / 13.75 QALY = $43,714/QALY	$470,583 / 10.29 QALY= $45,732 /QALY	$405,088 / 12.29QALY= $32,961/QALY
ICER	$43,926/ QALY	$98,679 / QALY	$45,033 / QALY	$57,433 / QALY
One-way SA	Hypoglycemia disutility decrease by 50% caused ICER to increase to 84,972 Otherwise, results stable and within original CI: • Varying baseline HbA1c from 7.6 to 9.5 ICER remained between $43,848 and $45,215 • % HbA1c reduction CGM vs SMBG =0.3 and 0.9 were $45,159and $42,552	ICER increased to $701,397 if benefit restricted to lowering glucose. If daily costs of CGM reduced from $13.85 to $9.89 the ICER drops below $70,000 If 2 test strips used per day CGM would be cost saving	Utility of diabetes with no complications, the annual cost of CHD, and the probability of going from diabetes with no complications to the CHD disease state, had the largest impact on the model. The utility of diabetes with no complications was decreased (increased) by 50%, the ICER over $300,000 ($30,000) /QALY. Annual cost of CHD also had a large impact on the model results, and when decreased (increased) by 50%, the ICER was US$86,000 ($12,000) / QALY.	Increasing the CGM sensor use to 51 sensors/year $58,044 Varying the number of SMBG tests/day from 7.1, though 6.1, to 2.1 resulted in the ICER of $74,292, $68,183, $43,751 / QALY Altering the baseline HbA1c value from 8.6% to 7.2% to 9% changed the ICER to $92,759 $53,693 /QLY respectively Increasing the rate of severe hypoglycemic events reduced the ICER to

Type 1 Studies:	Chaugule 2017[29]	Huang 2010[70]	McQueen 2011[99]	Roze 2014[131]
				$46,349 /QALY. Assuming no impact of fear hypoglycemia increased the ICER substantially (highest value reported; assuming a utility of 0.00552, decreased the ICER
Other SA	Presents an acceptability curve built from probabilistic model.	NR	Results from Monte Carlo Probabilistic model CGM: $494,135 (420,381 - 571,631) QALY=10.812 (9.894 - 11.887) SMBG: $470,583 (397,782 - 550,598) QALY=10.289 (9.615 - 10.957) 48% of the Monte Carlo simulations were under US$50,000/QALY, while 70% were under US$100,000/QALY	NR
Author's Conclusion	With a WTP threshold of $50,000 CGM was found to be a robustly, cost effective alternative to SMBG	Wide uncertainty with CI that included CGM dominating and being dominated by SMBG The immediate quality-of-life effect of CGM was responsible for the majority of projected lifetime benefits of the technology.	CGM was found to be cost effective in more circumstances than not, given a WTP of $100,000.	CGM is a cost–effective option in the treatment of Type 1 diabetes in Sweden
Limitations	• Canadian societal perspective stated but only direct costs reported • Sensitivity analyses related to long term impact of microvascular and	• Cardiovascular complications relied on type 2 diabetes cardiovascular models. • High baseline utilities effectively placed a ceiling on	• Some costs were extrapolated from studies that include all age groups. • RCT data provide information up to 12	• Swedish societal perspective • Limited acknowledgment of modeling/study limitations • Model assumes lifetime horizon; RCT data provide

Type 1 Studies:	Chaugule 2017[29]	Huang 2010[70]	McQueen 2011[99]	Roze 2014[131]
	macrovascular complications not presented • Model assumes lifetime horizon; RCT data provide information up to 12 months. Change in A1C based on DIAMOND trial; Unclear if 1% change with CGM use over lifetime is sustainable. • Industry funded	the potential quality-of-life benefit of CGM • Unclear if use of DCCT models for microvascular complications and type 1 DM models for cardiovascular complications reflect current care	months; sustainability of improved A1C unclear • Substantial variation in ICER estimates based on sensitivity analysis/modeling of diabetes complications based on probability evaluations from different populations	information up to 12 months. • Industry ties

Table 52. Overview of formal economic studies for T2DM.

Type 2 Studies:	Fonda 2016[49]
Population	Adults avg. age= 57.8 years. Diagnosis with type 2 diabetes for at least 3 months. Not taking prandial insulin. Initial A1C of between 7% and 12% Both MDI and CSII
Intervention(s)	CGM (intervention was short-term and intermittent)
Comparator(s)	SMBG
Country	USA (w/UK trial data)
Funding	Dexcom Grant
Study design	CUA
Perspective	Third-party payer (direct costs only)
Time horizon	Lifetime
Analytic model	Markov based (CORE Diabetes Model), Scenario analysis
Effectiveness outcome	Life expectancy (LE) QALY
Effectiveness outcome components	Assumed HbA1c reduction of 1.1 (±1.5) and 0.5 (±1.3) for CGM and SMBG respectively Hypoglycemia, amputation, a myocardial infarction, etc.), the progression of A1C, systolic blood pressure, lipids.
Source for effectiveness data	Risk adjustments are derived from the United Kingdom Prospective Diabetes Study (UKPDS)[2], the Diabetes Control and Complications Trial (DCCT), the Framingham Heart Study, and other published literature. CORE Diabetes Model
Costing year	2011
Currency	USD
Discounting	3%
Components of cost data	Intervention costs of CGM, SMBG, antidiabetic oral medications, insulin, routine management such as recommended screening, exams, and treatment for depression, and treatment of diabetes complications. cardiovascular disease complications, renal complications, acute events, eye disease, and neuropathy
Cost sources	Provided by Dexcom Inc. and published literature[2,102,117,151]
Sensitivity analysis	Both univariate and probabilistic sensitivity conduct. Minimal details reported.
QHES	75/100
Results:	
Cost / QALY of CGM	$66,094 /6.03 QALY =10,961
Cost / QALY of comparator(s)	$65,441 / 5.96 QALY = 10,980
ICER	$8,898 / QALY
One-way SA	Results not discussed
Other SA	Probabilistic cost-effectiveness analysis suggests that the likelihood of the intervention being cost-effective is 70% at the willingness-to-pay threshold of $100,000 per QALY.

Type 2 Studies:	Fonda 2016[49]
Author's Conclusion	CGM offers a cost-effective alternative to populations matching that the trial specifically: short-term, intermittent use in people with type 2 diabetes.
Limitations	• Small sample size of trial (n = 100) to estimate effectiveness parameters. • Limited sensitivity analyses presented. • Used older CGM device that has since been update. • Life-time horizon used; Few RCT data past available on long-term CGM use in type 2 DM. • Unclear if use of DCCT, USPKD and Framingham data for complications reflect current care

5. Strength of Evidence (SoE) Summary Tables

The following summaries of evidence have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by comparator. Details of other outcomes are available in the report.

5.1. Strength of Evidence Summary: Continuous Glucose Monitoring Efficacy Results

Notes:

- Only primary clinical and primary intermediate outcomes are were rated for strength of evidence
- Only time frames for which there is evidence are represented in the SoE tables

Strength of Evidence Summary: CGM versus SMBG efficacy results in <u>children</u> with type 1 diabetes

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
CHILDREN with T1DM								
Success (Achieving HbA1C% <7.0%)	3 mos	1 (N=113) JDRF 2008	No	Unknown	No	Yes[3] (-1)	GCM 25%, SMBG 6.9% RD -19%, 95% CI -32% to -5% <u>Conclusion</u>: Substantially more children in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW
	6 mos	2 (N = 251) JDRF 2008, Mauras 2012	No	No	No	Yes[3] (-1)	GCM 20.8%, SMBG 13.5% Pooled RD 7%, 95% CI -21% to 6%, I^2 = 50% <u>Conclusion</u>: No clear differences between CGM and SMBG.	⊕⊕⊕◯ MODERATE
	12 mos	2 (N = 309) Bergenstal 2010 Kordonuri 2010	No	No	No	Yes[3] (-1)	GCM 26.0%, SMBG 19.4% Pooled RD 7%, 95% CI -15% to 0%, I^2 =0%	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: No clear differences between CGM and SMBG.	
HbA1c%: Absolute reduction of ≥0.5%	3 mos. 6 mos	1 (N=113) JDRF 2008 2 (N = 141) JDRF 2008 Mauras 2012	No	3 mos Unknown 6 mos Yes	No	Yes[3] (-1)	3 months (1 trial) GCM 47%, SMBG 28% RD -20%, 95% CI -37% to -2%) 6 months (2 trials) GCM 35%, SMBG 31% Pooled RD -6%, 95% CI-37% to 25%, I^2 = 87% Conclusion: At 3 months, more children with CGM had an absolute reduction in HbA1c% of ≥ 0.5%, however at 6 months across two trials there was no difference in the pooled estimate and heterogeneity was substantial.	⊕⊕◯◯ LOW
HbA1c %: relative reduction of ≥10% from baseline	3, 6 months	1 (N=113) JDRF 2008	No	Unknown	No	Yes[3] (-1)	3 Months: RD -19%, 95% CI -34% to -4% 6 months: RD -17%, 95% CI -31% to -2% Conclusion: More children in the CGM group experienced ≥10% reduction at 3 and 6 months	⊕⊕◯◯ LOW
HbA1c % Mean between group difference in change from baseline	3mos	3 (N= 307) Kordonouri, Hirsch 2008, JDRF 2008	No	Yes[2] (-1)		Yes[3] (-1)	Pooled MD in change scores -0.22%, 95% CI -0.44% to 0.0%, I^2 = 3% Conclusion: Small reduction from baseline in mean HbA1c% favoring CGM was not statistically significant	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	6 mos	4 parallel RCTs (N = 445) Hirsch 2008, JDRF 2008 Kordonouri 2010 Mauras 2012 1 Crossover RCT (N=72) Battelino 2012	No	Yes[2] (-1)	No	No	Pooled MD in change scores: (4 parallel trials): -0.90, 95% CI -0.26 to 0.08; Cross-over trial: MD -0.46, 95% CI -0.26 to -0.66 Conclusion: There is no clear difference between CMG and SMBG across the parallel RCTs which provide the bulk of the evidence. One cross-over trial reported a significant difference during CMG periods: MD -0.46, 95% CI -0.26 to -0.66	⊕⊕⊕◯ MODERATE
	12 mos	2 (N=310) Bergenstal 2010, Kordonouri 2010	No	No	No	Yes[3] (-1)	Pooled MD in change scores: -0.31, 95% CI -0.99 to 0.36, I^2 = 73% Conclusion: There is no difference between CGM and SMBG based on pooled estimates; substantial heterogeneity is noted.	⊕⊕⊕◯ MODERATE
Hypoglycemia (≤70 mg/dL) Minute/day in range	3 mos, 6 mos	2 (N =239) JDRF 2008 Mauras 2012,	No	No	Yes[4] (-1)	Yes (-1)	**3 months:** Pooled WMD: -5.22, 95% CI -32.78 to 22.35 **6 months:** Pooled WMD: -11.09, 95% CI -30.16 to 7.99 Conclusion: There is no clear difference between CGM and SMBG at any time up to 6 months	⊕⊕◯◯ LOW
Hypoglycemia (<55 mg/dL)	3 mos, 6 mos	2 (N =239) JDRF 2008 Mauras 2012,	No	No	Yes[4] (-1)	No	**3 months:** Pooled WMD: -3.04, 95% CI-10.93 to 4.48	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Minute/day in range							**6 months:** Pooled WMD: -2.48 95% CI -10.49 to 5.53 <u>Conclusion:</u> There is no difference between CMG and SMBG at either time.	
Hypoglycemia (≤70 mg/dL) AUC	3, 6, 12 mos	3, 6 months 1 (N= 128) Mauras 2012) 12 mos 1(N=159) Bergenstal 2010	No	No	Yes[4] (-1)	No	CGM vs. SMBG **3 months:** 0.1 vs. 0.2 **6 months:** 0.1 vs. 0.2 **12 months:** 0.23 vs. 0.25, p = 0.790 <u>Conclusion:</u> There is no difference between CGM and SMBG at any time up to 12months	⊕⊕◯◯ LOW
<u>Severe Hypoglycemic events</u> (Events requiring assistance, resuscitative action, those resulting in loss of consciousness, seizure, or coma)	To 12 mos	4 trials (N = 517) JDRF 2008, Mauras 2012, Bergenstal 2010 Kondnouri 2010	No	No	No	Yes[3] (-2)	CGM vs. SMBG Number of events: 4.6% vs. 6.5%; pooled RD -1.2%, 95% CI -6% to 2.0%, I^2 = 22% <u>Conclusion across measures</u>: Severe hypoglycemia is a rare event and studies were likely underpowered to detect differences between treatments No apparent difference between CGM and SMBG with regard to the number of severe events; Similarly no difference between groups in the following measures: the proportion of children with ≥1 severe hypoglycemic events, number of severe hypoglycemic events with seizure, coma or loss of consciousness or incidence of	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							severe hypoglycemia at any time frame..	

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: CGM versus SMBG efficacy results in adults with type 1 diabetes

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
ADULTS with T1DM								
Success (Achieving HbA1C% <7.0%	3 months	2 (N=253) Beck 2017, JDRF 2008	No	Yes[2] (-1)	No	Yes[3] (-1)	CGM 23%, SMBG 8.2% Pooled RD -18%, 95% CI -40% to 3.0%, I^2 = 81% Conclusion: More adults in the CGM group achieved success vs. SMBG; while pooled results did not reach statistical significance, results from individual trials did. Substantial heterogeneity is noted.	⊕⊕◯◯ LOW
	6 months	3 (N=328) Beck 2017, JDRF 2008, Hermanides 2011		Yes[2] (-1)		Yes[3] (-1)	CGM 25.4%, SMBG 4.4% Pooled RD -23%, 95% CI -36% to -10%, I^2 = 67% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW
	12 months	1 (N=329) Bergenstal 2010	No	Unknown	No	Yes[3] (-1)	CGM 34% , SMBG 11.7% RD -23%, 95% CI -31% to -14% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW
HbA1c %: Absolute reduction of ≥0.5	3 months	2 (N=243) JDRF 2008, New 2015	No	No	No	Yes[3] (-1)	CGM 32.9%, SMBG 14.9% Pooled RD -18%, 95% CI -28% to -8%, I^2 = 0% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕⊕◯ MODERATE
	6 months	1 (N=114) JDRF 2008	No	Unknown	No	Yes[3] (-1)	CGM 48%, SMBG 11% RD -37%, 95% CI -54% to -21% Conclusion: More adults in the CGM group achieved success vs. SMBG	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
HbA1c %: relative reduction of ≥10% from baseline	3, 6 months	2 (N=353) Beck 2017, JDRF 2008	No	3 months Yes[2] (-1) 6 months: No*	No	Yes[3] (-1)	**3 months:** CGM 48.4%, SMBG 18.4% Pooled RD -25%, 95 CI% -50% to 0%, I^2 = 82% **6 months:** CGM 46.7%, SMBG 12.1% Pooled RD -30%, 95% CI -46% to -13%, I^2 =64% Conclusion: More adults in the CGM group achieved success vs. SMBG at both timepoints; however, the results at 3 months are marginally significant	3 months ⊕⊕◯◯ LOW 6 months ⊕⊕⊕◯ MODERATE
HbA1c % Mean between group difference in change from baseline	3-4 months	6 (N=599) Beck 2017, Hermanides 2011, Hirsch 2008, JDRF 2008, New 2015, Peyrot 2009	No	Yes[2] (-1)	No	Yes[3] (-1)	Pooled MD in change scores: : -0.43%, 95%CI -69% to -19%, I^2=76% Conclusion: CGM use was associated with clinically and statistically significant improvement in mean HbA1c % compared with SMBG	⊕⊕◯◯ LOW
	3 months	Flash CGM 1 (N=239) Bolinder	Yes[1]	Unknown	No	Yes[3] (-1)	FCGM 0.1% (SD 0.6), SMBG 0.1% (SD0.7%) MD 0%, 95% CI -0.17% to 17% Conclusion: No differences between FCGM and SMBG	⊕◯◯◯ INSUFFICIENT
	6 months	4 (N = 429) Beck 2017, Hermanides 2011, Hirsch 2008, JDRF 2008,	No	Yes[2] (-1)	No	Yes[3] (-1)	Pooled MD in change scores -0.52%, 95% CI -0.84% to -0.19%, I^2 = 84% Conclusion: CGM use was associated with clinically and statistically significant improvement in HbA1c % compared with SMBG	⊕⊕◯◯ LOW
		Flash CGM 1 (N = 239) Bolinder	Yes[1]	Unknown	No	Yes[3] (-1)	FCGM 0.2% (SD0.6) SMBG 0.2% (SD 0.7) MD 0%, 95% CI -0.17% to 17%	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: No differences between FCGM and SMBG	
	12 months	1 (N=329) Bergenstal 2010	No	Unknown	No	Yes[3] (-1)	Pooled MD in change scores: 0.6%, 95% CI -0.76% to -0.44% Conclusion: CGM use was associated with clinically and statistically significant improvement in HbA1c % compared with SMBG	⊕⊕◯◯ LOW
HbA1c % Mean difference at follow-up	Longest follow-up†	Parallel RCTs 6 (n= 785) JDRF 2008, Bergenstal 2010, Hirsch 2008, Hermanides 2011, Peyrot 2009 Beck 2017, New 2015 Cross-over trials 4 (N = 305) Battelino 2012, Lind 2017 vanBeers 2016, Langeland 2012	No	Yes[2] (-1)	No	Yes[3] (-1)	Parallel trials (6 trials, N=785) Pooled MD -0.48, 95% CI -0.7 to -0.28, I^2 = 79% Cross-over trials (26 week treatment period, 2 trials, N=223) Pooled MD -0.42, 95% CI -0.51 to -0.33, I^2 = 0% Cross-over trials (4-16 week treatment, 2 trials (N=82) Pooled MD 0.06, 95% CI -0.05 to 0.16, I^2 = 0% Conclusion: Across trials, the bulk of the evidence suggests clinically meaningful improvement in mean HbA1c % with CGM versus SMBG.	⊕⊕◯◯ LOW
# of hypoglycemic events (standardized per day in parallel trial, events/week in cross-over trial)	Parallel trial 6 mos Cross-over trial 4 month treatment periods	Parallel 1 RCT (N = 71) Hermanides Crossover 1 (n=52) vanBeers	No	Yes[2] (-1)	Yes[4] (-1	Yes[3] (-1)	Parallel trial CMG 0.7 ± 0.7 SMBG 0.6 ± 0.7 MD 0.1, 95% CI -0.2 to 0.5 Crossover trial Events/week(CGM-derived data): 10.1 (8.7 to 11.4) vs. 11.1 (9.8 to 12.5), MD -1.1, 95% CI -1.4 to -0.8	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: There is no clear difference between CGM and SMBG in one parallel trial; one cross-over trial reported fewer events per week during CGM phases; the clinical significance of these findings is unclear.	
Hypoglycemia (<70 mg/dL) Minute/day in range, hours/day or % of time spent in range, # of events	Parallel 3, 6 mos Cross-over, 4, 6 mos treatment periods	Parallel, 4 RCTs (N=448) JDRF 2008, Beck 2017, New 2015 Hemanides 2011 Cross-over RCTs 2 (N=213) Lind 2017, vanBeers 2016	No	No	Yes[4] (-1)	Yes[3] (-1)	Parallel trials: Minutes per day **3 months** (2 trials, N=377): pooled MD -21.45 minutes, 95% CI -36.31 to -6.59, I^2 = 0%; **6 months** (2 trials, N=248): pooled MD -19.66 minutes, 95% CI -37.85 to -1.47, I^2 = 20% 1 Parallel trial (N = 71, <72mg/dL), 6 months: % time during monitoring: MD 0.2, 95% CI -1.4 to 1.9, p= 0.79; standardized number of events/day: MD 0.1 (-0.2 to 0.5, p = 0.40) 1 Cross-over trial (N=52): Hours per day across 16 week treatment periods: CGM 1.6 vs. SMBG 2.7 MD -1.1, 95% CI -1.4 to -0.8, p<0.0001; CGM-derived events/week: MD -1.1, 95% CI -0.14 to -0.8 1 Cross-over trial (N=142): % of time across 26 week treatment periods: CGM 2.79% ± 2.97% vs. 4.79% ± 4.03%, p <0.0001; MD -2.0, 95% CI -2.83 to -1.17 Conclusion: Across most parallel and cross-over trials, CGM appears to be associated with decreased time spent in	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							the hypoglycemic range ≤70 mg/dL compared with SMBG.	
Hypoglycemia (≤70 mg/dL) Hours/day Number of events	3, 6 months	Flash CGM 1(N = 239) Bolinder 2016	Yes (-1)	Unknown	Yes[4] (-1)	No	Hours/day, adjusted MD (SE) 3 months: MD -1.09 (0.18) 6 months: MD -1.24 (0.24) # of events, adjusted MD (SE) 3 months: MD -0.35 (0.09) 6 months: MD -0.45 (0.09) Conclusion: In 1 trial, FCGM appears to be associated with decreased time spent in the hypoglycemic range ≤70 mg/dL and number of events compared with SMBG	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (≤55 mg/dL) Minutes per day	3, 6 months	2 (N = 249) JDRF 2008, Beck 2017	No	3 months No 6 months Yes[2] (-1)	Yes[4] (-1)	Yes[3] (-1)	**3 months:** Pooled MD -14.2 minutes, 95% CI -23 to -5.4 I^2=38% **6 months:** Pooled MD-13.1 minutes, 95% CI-30.4 to 4.25, I^2= 90% Conclusion: As small decrease in the mean minutes per day spent in this range favoring CGM was seen at 3 months, but was no longer significant at 6 months where substantial heterogeneity was noted; results from the newest trial failed to reach statistical significance.	3 months ⊕⊕◯◯ LOW 6 months ⊕◯◯◯ INSUFFICIENT
Hypoglycemia (≤55 mg/dL) Hours per day, number of events	3, 6 months	FCGM 1 RCT (N = 239) Bolinder	Yes[1]	Unknown	Yes[4] (-1)	Yes[3] (-1)	Hours per day: **3 months:** adjusted MD -0.68, SE 0.13 **6 months:** adjusted MD -0.82, SE 0.74 Events **3 month:** adjusted MD -0.33, SE 0.06,	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							6 month: adjusted MD -0.38, SE 0.74 Conclusion: In 1 trial FCGM appears to be associated with decreased time spent in the hypoglycemic range ≤55 mg/dL fewer events compared with SMBG	
Severe hypoglycemia proportion of adults with ≥1 severe hypoglycemic event; number of events (Most trials defined as events requiring assistance or loss of consciousness)	Parallel 3-12 mos Crossover treatment periods of 4-26 weeks	Parallel 1 (N = 152) Beck 2017 3 Cross-over vanBeers 2016 (N= 52) Lind (N =161) Langeland (N=30)	No	No	No	Yes[3] (-2)	Parallel Trials: Proportion of adults with ≥1 severe hypoglycemic events: 3 trials, pooled RD 0%, 95% CI -4% to 4%, I^2=0% Number of severe hypoglycemic events: 4 trials, pooled RD 0%, 95% CI-6% to 7%, I^2=46% Crossover trials: Proportion with ≥1 severe hypoglycemic event (1 trial, N = 52), adjusted OR 0.48, 95% CI 0.2 to 1.0, p=0.062; Number of events: Largest trial (n=161) CGM vs. SMBG phases, 1 event (0.04 per 1000 patient-years) vs. 5 events (0.19 per 1000 patient-years), p =0.7545; one small trial (N = 52) reported, fewer total events during CGM phases (14 vs. 34 events, p = 0.033); Mean number of episodes per 4 week treatment period (1 trial N=30) MD 0.9, 95% I -0.18 to 1.98, p=0.6 Conclusion: Studies were likely underpowered to detect differences between groups. Across parallel and cross-over trials there is no statistical difference between CGM and SMBG with regard to the proportion of adults with ≥1 severe hypoglycemic events. With regard to the number of events the bulk of	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							evidence (4 parallel trials, 3 crossover trials) no statistical difference between groups for the number of severe hypoglycemic events was seen.	
Hypoglycemic severe adverse events; proportion of patients and number of events (appears to be defined as those requiring 3rd party assistance)	6 months	FCGM 1 RCT (N = 239)	Yes[1]	Unknown	No	Yes[3] (-2)	FCGM 2% (n =2), SMBG 2% (n=3) of patients Number of events FCMG, 2, SMBG 4 Conclusion: There is insufficient evidence to draw conclusions; study was likely underpowered to detect rare events.	⊕◯◯◯ INSUFFICIENT
Nocturnal hypoglycemia; median percent of time spent at night in range, CGM-derived events	Parallel trial:6 mos, Crossover across both 16 week periods	Parallel 1 (N = 152) Beck 2017 Cross-over 1 (N= 52) vanBeers 2016	No	<70mg/dL No <50 mg/dL Unknown	Yes[4] (-1)	< 70mg/dL Yes[3] (-1) <50mg/dL Yes[3] (-2)	CGM vs. SMBG <u>Parallel trial 6 months median % (IQR), effect estimates NR</u>: <70mg/dL median % (IQR): 1.8% (0.1% to 5.8%) vs. 5.2% (0.9% to 9.4%), p=0.003 <50 mg/dL: 0% (0% to 0.9%) vs. 0.3% (0% to 2.4%), p=0.001 <u>Cross-over trial, across both 16 week treatment periods, <70mg/dL:</u> % of time: 7.6% (95% CI 5.3% to 9.8%) vs. 13.3% (95% CI 11.0% to 15.5%); MD -5.7% 95% CI -8.2% to -3.2% CGM derived events/night: 0.26 (0.21 to 0.31) vs. 0.33 (0.28 to 0.38); MD -0.07, 95% CI -0.11 to -0.02	<70mg/dL ⊕⊕◯◯ LOW <50mg/dL ⊕⊕⊕◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: Across parallel and cross-over trials, CGM appears to be associated with decreased time spent in the hypoglycemic ranges at night compared with SMBG, however, the clinical significance of the effect size is unclear.	
Nocturnal hypoglycemia; Mean Time in range Mean # of events	6 months	FCGM 1 RCT (N = 239)	Yes[1]	Unknown	Yes[4] (-1)	Yes[3] (-1)	<70mg/dL, hrs/day adjusted MD (SE) **3 months**: -0.48 (0.10) **6 months:** -0.47 (0.12) Events: adjusted MD (SE) **3 months:** -0.11 (0.03) **6 months:** -0.14 (0.03) <55 mg/dL, hrs/day adjusted MD (SE) **3 months:** -0.68 (0.13) **6 months:** -0.82 (0.175) Events: adjusted MD (SE) **3 months:** -0.33 (0.06) **6 months:** -0.38 (0.074) Conclusion: FCGM was associated with less time in the hypoglycemic ranges and fewer events.	⊕⊕⊕◯ INSUFFICIENT

* Effect size are in the same direction

†Results based on longest reported follow-up for parallel trials (range 3-12 months); for cross-over trials, time is length of treatment periods (e.g. CGM phase, SMBG phase)

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: CGM versus SMBG efficacy results in mixed populations of adults and children with type 1 diabetes

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Mixed populations T1DM								
Success (Achieving HbA1C <7.0%)	3 mos	3 (N=296) JDRF 2008 O'Connell 2009 Hirsch 2008	No	Yes[2] (-1)	No	Yes[3] (-1)	CGM 30 %, SMBG 11.3% Pooled RD -19%, 95% CI -32% to -7%, I^2=49% Conclusion: significantly more patients in the CGM group achieved success compared with SMBG	⊕⊕◯◯ LOW
	6 mos	2 (N = 251) JDRF 2008 Hirsch 2008	Yes[1] (-1)	No	No	Yes[3] (-1)	CGM 16.9%, SMBG 21.4% Pooled RD 4%, 95% CI -6% to 14%, I^2= 0% Conclusion: No difference between groups.	⊕⊕◯◯ LOW
HbA1c %: Absolute reduction of ≥0.5% OR relative reduction of ≥10% from baseline	3, 6 months	1 (N=107) JDRF 2008	No	Unknown	No	Yes[3] (-1)	Absolute reduction ≥0.5%: CGM 35.7% , SMBG 37.3 % RD 14%, 95% CI-33% to 4% Relative reduction, ≥10%: CGM 14% , SMBG 9.8% RD 4%, 95% CI-17% to 8% Conclusion: No difference between groups.	⊕⊕◯◯ LOW
HbA1c % Mean between group differences in A1c change from baseline	3 mos	Parallel trials 3 (N=269) JDRF 2008, Deiss 2006, O'Connell 2009	No	No	No	Yes[3] (-1)	Pooled MD in change scores -0.25%, 95% CI -0.48% to -0.02%%, I^2 = 28% Conclusion: Small reduction from baseline in mean HbA1c % favoring CGM, but may not be clinically important	⊕⊕⊕◯ MODERATE
	6 mos	Parallel 4 (N=495)	No	No	No	Yes[3] (-1)	Parallel trials: Pooled MD in change scores: -0.19%, 95% CI -0.34% to -0.04%	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
		JDRF 2008, JDRF 2009, Battelino 2011, Raccah 2009 Crossover trial across 6 month treatment periods, 1 (n = 153)					1 Crossover trial: MD across periods: -0.43, 95% CI -0.32 to -0.55 <u>Conclusion</u>: Small reduction from baseline in mean HbA1c % favoring CGM, but may not be clinically important	
Severe Hypoglycemic events proportion of patients with ≥ 1 severe hypoglycemic events at any time frame; Number of severe events	Up to 6 months	6 (N=656) Diess 2006, O'Connell 2009, JDRF 2008, JDRF 2009, Battelino 2011, Hirsch 2008	No	No	No	Yes[3] (-2)	<u>Patients with ≥ 1 event</u> CGM 5.7% , SMBG 4.6% Pooled RD 1%, 95% CI -2% to 3%, I^2= 0% <u>Number of events</u> CGM 7.9%, SMBG 5.8% Pooled RD 1%, 95% CI- 2% to 3%, I^2= 29% <u>Conclusion</u>: Studies were likely underpowered to detect a difference between groups. No difference between groups for either outcome.	⊕⊕◯◯ LOW
Severe Hypoglycemia events requiring assistance or intervention	Parallel trials -3 months Cross-over 6 months	Parallel 3 (N =351) JDRF 2008, JDRF 2009, Raccah Crossover 1(N=153) Battelino 2012	No	No	No	Yes[3] (-2)	Parallel Trials: CGM 3.4%, SMBG 2.9% Pooled RD 1%, 95% CI -3% to 3%, I^2=9% Crossover trial: events (rate) CGM 4 (5.7 per 100 patient-years) SMBG 2 (2.83 per 100-patient-years) P=0.40 <u>Conclusion</u>: Studies were likely underpowered to detect a difference between groups .No difference between groups	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Nocturnal Hypoglycemia	6 months	1 (N =116) Battelino 2011	No	Unknown	Yes[4] (-1)	Yes[3] (-2)	CGM vs. SMBG (mean, SD) <55 mg/dL: 0.13 (0.30) vs. 0.19 (0.19), p=0.01 <63 mg/dL: 0.21 (0.32) vs. 0.30 (0.31), p=0.009 <u>Conclusion:</u> CGM was associated with fewer mean number of excursions vs. SMBG, <55 mg/dL and < 63 mg/dL; large standard deviations (substantial variability) are noted calling estimate stability into question. The clinical importance of these findings is unclear	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (<70 mg/dL)	3, 6 months	6 (N=645) JDRF 2008, JDRF2009, Battelino 2011, O'Connell 2009, Raccah 2009, Hirsch 2008	Yes[1] (-1)	No	Yes[4] (-1)	Yes[3] (-1)	<u>Minutes per day</u> **3 months:** Pooled MD (2 trials, N= 226): -12.2, 95% CI-40.59 to 16.23, I^2=0% **6 months:** Pooled MD (4 trials N = 445)**:** -16.26, 95% CI-32.16 to -0.37, I^2=21% <u>% of time spent in range, 1 RCT (N= 55), 3 months</u> MD 0.54, 95% CI -3.5 to 4.6 <u>Mean number of events, 2 RCTs (N= 254), 6 months:</u> CGM 0.83 ± 0.73 vs. SMBG 0.84 ± 0.73 (1 trial) Ratio of means (1 trial): 0.70 (0.43 to 1.03) <u>Change in baseline # events per day, 1 RCT (N=100), 6 months</u> MD 0.0, 95% CI -0.3% to 0.3% <u>Conclusion:</u> There were no differences in number of events, minutes/day or percent of time spent in this range between CGM and SMBG at 3 months. A 16 minute difference favoring CGM was seen across four trials at 6 months. The clinical significance of the effect size is not clear.	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Time spent in hypoglycemic range < 55 mg/dL (min/day)	3, 6 months	3 months 2 (n=226) JDRF 2008, JDRF 2009 6 months 3 (N=345) JDRF 2008, JDRF 2009, Battelino 2011	No	No	Yes[4] (-1)	Yes[4] (-1)	**3 months:** (2 trials) MD -7.83, 95% CI -15.92 to 0.26, I^2 = 0% **6 months:** (3 trials): MD -7.26, 95% CI-16.14 to 1.62, I^2 = 51% Conclusion: There were no differences minutes/day between CGM and SMBG at 3 or 6 months.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: CGM versus SMBG efficacy results in adults with type 2 diabetes

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
T2DM								
Success (Achieving HbA1c% <7.0%)	3 and 6 months	1 (N=152 at 3 months; N= 158 at 6 months) Beck 2017[b]	No	Unknown	No	Yes[3] (-1)	**3 months:** CGM 22%, SMBG 12% Adjusted RD: 10%, 95% CI −2% to 23% **6 months:** CGM 11%, SMBG 9%	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Adjusted RD: 3%, 95% CI −9% to 14% Conclusion: There is no clear difference at 3 months; no difference between groups at 6 months.	
HbA1c %: Absolute reduction of ≥0.5% OR Relative reduction of ≥10% from baseline	3 and 6 months	1 (N=152 at 3 months; N= 158 at 6 months) Beck 2017[b]	No	Unknown	No	Yes[3] (-1)	Absolute reduction **3 months:** CGM 61%, SMBG 38% Adjusted RD: 31%, 95% CI 5% to 57% **6 months:** CGM 56%, SMBG 37% Adjusted RD: 26%, 95% CI 0% to 50% Relative reduction **3 months:** CGM 44%, SMBG 26% Adjusted RD: 25%, 95% CI 3% to 46% **6 months:** CGM 40%, SMBG 24% Adjusted RD: 22%, 95% CI 0% to 42% Conclusion: Significantly greater proportion of CGM vs. SMBG subjects achieved both an absolute (≥0.5%) and a relative (≥10%) reduction in HbA1c at both timepoints. Confidence intervals were wide.	⊕⊕◯◯ LOW
HbA1c % (mean change from baseline)	3 months	3 (N=309) Beck 2017, Vigersky 2012, Yoo 2008	No	No	No	Yes[3] (-1)	Pooled MD in change: -0.49%, 95% CI -0.71% to -0.26%, I^2 = 0% Conclusion: Clinically and statistically significant reduction with CGM versus SMBG	⊕⊕◯◯ MODERATE
	6 months	3 (N=308) Beck 2017[b], Tildesley 2013, Vigersky 2012,	Yes[1] (-1)	No	No	Yes[3] (-1)	Pooled MD in change: -0.37% (95% CI -0.59% to -0.14%) Conclusion: Statistically significant reduction with CGM versus SMBG	⊕⊕◯◯ LOW
		Flash CGM 1 (N=224) Haak 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	CGM 8.37% (SD 0.83%), SMBG 8.34% (SD 1.14%) adjusted MD at follow-up: 0.03 (SE 0.114), p=0.822	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: No differences between FCGM and SMBG.	
	9.5 and 12 months	1 (N=100) Vigersky 2012	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	**9.5 months** MD in change -0.30, 95% CI -0.77 to 0.17 **12 months** MD in change -0.40, 95% CI -0.89 to 0.09 Conclusion: Small reduction at both timepoints with CGM versus SMBG; however the difference was not statistically significant and may not be clinically meaningful.	⊕◯◯◯ INSUFFICIENT
Hypoglycemia (<50 mg/dl): minutes/day, % of time or % of SMBG readings/day in range **Flash CGM: minutes per day and episodes in range <55 mg/dl**	3 months	2 (N=242) Beck 2017[b], Ehrhardt 2011	No	No	Yes[4] (-1)	Yes[3] (-1)	Minutes per day, median (IQR) (1 trial): CGM 0 (0-0) vs. SMBG 0 (0-3), p=ns % of time, median (IQR) (1 trial): CGM 0 (0-0) vs. SMBG 0 (0-0), p=ns % readings per day, mean (1 trial): CGM 1.9% vs. SMBG 2.7%, p=ns Conclusion: No statistically significant difference between groups.	⊕⊕◯◯ LOW
	6 months	1 (N=146) Beck 2017[b]	No	Unknown	Yes[4] (-1)	No	Minutes per day, median (IQR): CGM 0 (0-1) vs. SMBG 0 (0-5), p=ns % of time, median (IQR): CGM 0 (0-0) vs. SMBG 0 (0-0.3), p=ns Conclusion: No statistically significant difference between groups.	⊕⊕◯◯ LOW
		Flash CGM 1 (N=224)	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	Minutes per day in range <55 mg/d: CGM 11.4 (SD 22.2), SMBG 22.2 (SD 41.4)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
		Haak 2016					Adjusted MD at follow-up: -13.2 minutes (SE 4.1), p=0.0014 % difference CGM vs. SMBG: -53.1% Events per day (<55 mg/dl), mean (SD) CGM 0.14 (0.24), SMBG 0.24 (0.36); Difference in adjusted means: -0.12 (SE 0.037), p=0.002 % difference CGM vs. SMBG: -44.3% Conclusion: Statistically fewer minutes and episodes per day spent in hypoglycemic range <55 mg/dl in the CGM vs. SMBG group.	
Hypoglycemia (<70 mg/dl): minutes/day, % of time or % of SMBG readings/day in range	3 months	2 (N=242) Beck 2017[b], Vigersky 2012	No	No	Yes[4] (-1)	Yes[3] (-1)	Minutes per day, median (IQR) (1 trial): CGM 9 (1-25) vs. SMBG 11 (0-37), p=ns % of time, median (IQR): CGM 0.3 (0-1.5) vs. SMBG 0.6 (0-2.3), p=ns % readings per day, mean (1 trial): CGM 3.6% vs. SMBG 2.7%, p=ns Conclusion: No statistically significant difference between groups.	⊕⊕◯◯ LOW
	6 months	1 (N=146) Beck 2017[b]	No	Unknown	Yes[4] (-1)	No	Minutes per day, median (IQR): CGM 4 (0-17) vs. SMBG 12 (0-34), p=ns % of time, median (IQR): CGM 0.3 (0-1.0) vs. SMBG 0.3 (0-2.3), p=ns Conclusion: No statistically significant difference between groups.	⊕⊕◯◯ LOW
		Flash CGM 1 (N=224) Haak 2016	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	Minutes per day: CGM 35.4 (SD 49.2), SMBG 59.4 (SD 77.4)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Difference in adjusted means at follow-up: -28.2 minutes (SE 8.0), p=0.0006 % difference CGM vs. SMBG: -43.1% <u>Events per day (<70 mg/dl), mean (SD)</u> CGM 0.38 (0.45), SMBG 0.53 (0.59); Difference in adjusted means: -0.16 (SE 0.065), p=0.016 % difference CGM vs. SMBG: -27.7% <u>Conclusion</u>: Statistically fewer minutes and episodes per day spent in hypoglycemic range <70 mg/dl in the CGM vs. SMBG group.	
	12 months	1 (N=92) Vigersky 2012	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	% readings per day, mean: CGM 3.6% vs. SMBG 2.5%, p=ns <u>Conclusion</u>: No statistically significant difference between groups.	⊕○○○ INSUFFICIENT
Nocturnal Hypoglycemia (<50 and <70 mg/dl): % of time spent in range **Flash CGM: minutes per night and episodes (within 7 hours) in range <70 mg/dl <55 mg/dl**	3, 6 months	1 (N=151 at 3 months, N=146 at 6 months) Beck 2017[b]	No	Unknown	Yes[4] (-1)	No	<u>% of time, <50 mg/dl, median (IQR):</u> 3 and 6 months: CGM 0 (0-0) vs. SMBG 0 (0-0), p=ns <u>% of time, <70 mg/dl, median (IQR):</u> 3 months: CGM 0.2 (0-1.8) vs. SMBG 0 (0-1.8), p=ns 6 months: CGM 0 (0-1.6) vs. SMBG 0 (0-2.9), p=ns <u>Conclusion</u>: No statistically significant difference between groups at 3 and 6 months for both measures.	⊕⊕○○ LOW
	6 months	Flash CGM 1 (N=224) Haak 2016	Yes[1] (-1)	Unknown	Yes[4] (-1)	Yes[3] (-1)	<u>Minutes per night <55 mg/dl</u>: CGM 13.8 (SD 25.8), SMBG 30.6 (SD 43.2)	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Difference in adjusted means at follow-up: -17.4 minutes (SE 4.8), p=0.0001 % difference CGM vs. SMBG: -54.3% <u>Events at night (<55 mg /dl)</u> CGM 0.06 (0.13), SMBG 0.13 (0.21); Difference in adjusted means: -0.07 (SE 0.02), p=0.001 % difference CGM vs. SMBG: -53.0% <u>Minutes per night <70 mg/dl</u>: CGM 5.4 (SD 13.2), SMBG 11.4 (SD 24) Difference in adjusted means at follow-up: -7.2 minutes (SE 2.4), p=0.0032 % difference CGM vs. SMBG: -58.1% <u>Events at night (<70 mg /dl)</u> CGM 0.14 (0.420), SMBG 0.27 (0.33); Difference in adjusted means: -0.12 (SE 0.03), p=0.0003 % difference CGM vs. SMBG: -44.9% <u>Conclusion</u>: Statistically fewer minutes and episodes per night spent and in hypoglycemic ranges <55 and <70 mg/dl in the CGM vs. SMBG group.	
Episodes of severe hypoglycemia	3-6 months	3 (N=264) Beck 2017[b], Tildesley 2013, Yoo 2008	No	No	No	Yes[3] (-2)	No episodes of severe hypoglycemia, defined as an event requiring assistance from another person, were reported in either group in one trial (Beck 2017[b]) over 6 months. Two trials did not define severe hypoglycemia; one stated that no clinically symptomatic hypoglycemic events occurred over 3 months and the second trial reported that severe hypoglycemia in both the CGM	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							and SMBG group was negligible with no serious events (data not provided, 6 month follow-up). Conclusions: Severe hypoglycemia is a rare event and trials were likely underpowered to detect differences between groups. No differences between groups in the frequency of severe hypoglycemic events.	
	6 months	Flash CGM 1 (N=224) Haak 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Three CGM (2%) patients (3 events) and one SMBG (1%) patient (1 event) experienced a severe hypoglycemic event (an event requiring third party assistance). Conclusions: There is insufficient evidence to draw conclusions; study was likely underpowered to detect rare events.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: CGM versus SMBG efficacy results in women with type 1 diabetes during pregnancy

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Pregnancy T1DM								
Gestational age (weeks)	up to 36 gestational weeks	2 (N=324) Feig 2017, Secher 2013	No	No	No	Yes[3] (-1)	Pooled MD: -0.08 weeks, 95% CI -0.65 to 0.48, I^2 = 54% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕○ MODERATE
Birthweight (grams)	up to 36 gestational weeks	2 (N=323) Feig 2017, Secher 2013	No	No	No	Yes[3] (-2)	Pooled MD: 51.7 grams, 95% CI -132.22 to 235.67, I^2 = 36% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕○ MODERATE
Miscarriage	up to 36 gestational weeks	2 (N=334) Feig 2017, Secher 2013	No	No	No	Yes[3] (-1)	CGM 4.8%, SMBG 3.0% Pooled RD: 2.0%, 95% CI -2.0% to 6.0%, I^2 = 0% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕○ MODERATE
Caesarean Section	up to 36 gestational weeks	2 (N=325) Feig 2017, Secher 2013	No	No	No	Yes[3] (-1)	CGM 50.9%, SMBG 62.3% Pooled RD: -11.0%, 95% CI -21.0% to -1.0%, I^2 = 0% Conclusion: Statistically fewer caesarean sections in women using CGM vs. SMBG.	⊕⊕⊕○ MODERATE
Preterm delivery	up to 36 gestational weeks	2 (N=325) Feig 2017, Secher 2013	No	No	No	Yes[3] (-1)	CGM 31.3%, SMBG 34.0% Pooled RD: -2.0%, 95% CI -12.0% to 8.0%, I^2 = 0% Conclusion: No difference between CGM vs. SMBG.	⊕⊕⊕○ MODERATE
Preeclampsia	up to 36 gestational weeks	2 (N=325) Feig 2017, Secher 2013	No	No	No	Yes[3] (-1)	CGM 8.6%, SMBG 14.2% Pooled RD: -5.0%, 95% CI -13.0% to 4.0%, I^2 = 34% Conclusion: No clear difference between CGM vs. SMBG.	⊕⊕⊕○ MODERATE

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Large for gestational age	up to 36 gestational weeks	2 (N=323) Feig 2017, Secher 2013	No	Yes (-1)	No	Yes[3] (-1)	Point estimates differed between trials: MD 0.13, 95% CI -0.05, 0.30 (Secher) MD -0.16, 95% CI -0.29, -0.03 (Feig) Pooled RD: -2.0%, 95% CI -30.0% to 26.0%, I^2 = 85% Conclusion: Effect sizes for the two trials were in the opposite direction; one trial favored CGM the other did not. No clear difference between CGM and SMBG. Pooled estimate did not reach significance; significant heterogeneity was noted.	⊕⊕◯◯ LOW
Severe Neonatal Hypoglycemia:2-hour plasma glucose <45 mg/dl and/or requiring IV glucose infusion	up to 36 gestational weeks	2 (N=317) Feig 2017, Secher 2013	No	Yes (-1)	No	Yes[3] (-1)	CGM 15.3%, SMBG 23.8% Pooled RD: -7.0%, 95% CI -19.0% to 4.0%, I^2 = 46% Conclusion: No clear difference between CGM vs. SMBG in either outcomes. One trial showed a significant benefit for CGM while the other trial showed no significant difference between groups.	⊕⊕◯◯ LOW
Severe Maternal Hypoglycemia: episode requiring a third party intervention	up to 36 gestational weeks	2 (N=304) Feig 2017, Secher 2013	No	Unknown	No	Yes[3] (-1)	1 trial, N=207 (Feig) CGM 10.7%, SMBG 11.5% (18 vs. 21 episodes, respectively) RD 1.0%, 95% CI -9.0% to 8.0% The second trial reported that 19 (16%) women experienced 59 severe hypoglycemic events, with no difference between the arms (data not provided). Conclusion: No statistical difference between groups.	⊕⊕◯◯ LOW
Neonatal hypoglycemia (2-hour plasma	up to 36 gestational weeks	1 (N=118) Secher 2013	No	Unknown	No	Yes[3] (-1)	CGM 37%, SMBG 45% RD -8.2% (95% CI -25.9% to 9.6%)	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
glucose <45 mg/dl)							Conclusion: No clear difference between groups for neonatal hypoglycemia.	
Episodes of maternal hypoglycemic (CGM levels <63 mg/dl for at least 20 minutes; distinct events counted only if separated by ≥30 minutes)	34 weeks gestation	1 (N=154) Feig 2017	No	Unknown	No	Yes[3] (-1)	Median (IQR) CGM 0.5 (0.3-0.8), SMBG 0.5 (0.3-0.8) Conclusion: No difference between CGM vs. SMBG.	⊕⊕◯◯ LOW
Major anomalies	up to36 gestational weeks	2 (N=334) Feig 2017, Secher 2013	No	Unknown	No	Yes[3] (-2)	Congenital anomalies occurred in two (1.9%) and three (2.8%) infants in the CGM and SMBG groups, respectively, as reported by one trial (Feig), and consisted of aortic stenosis and hypospadias grade 1 (CGM group) and hypoplastic right heart syndrome (termination of pregnancy), aberrant right subclavian artery, and bilateral hydronephrosis (SMBG group) The other trial reported that two infants (1.6%) had major congenital malformations: one ventricular septal defect combined with coarctation of the aorta and one congenitally corrected transposition of the great arteries; however the authors did not report to which group these women were randomized. Conclusion: Major anomalies are likely rare events. Insufficient evidence precludes firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Stillbirth	34 gestations weeks	1 (N=211) Feig 2017	No	Unknown	No	Yes[3] (-2)	CGM 0%, SMBG 0.9% RD -0.9%, 95% CI -2.8 to 0.9% Conclusion: No statistical difference between CGM vs. SMBG.	⊕⊕◯◯ LOW
Birth trauma (to include shoulder dystocia)	34 gestations weeks	1 (N=200) Feig 2017	No	Unknown	No	Yes[3] (-2)	CGM 2%, SMBG 0% RD 2%, 95% CI not calculable, p=0.16 Conclusion: No difference between CGM vs. SMBG.	⊕⊕◯◯ LOW
Admission to neonatal intensive care unit (NICU) (>24 hours)	34 gestations weeks	1 (N=200) Feig 2017	No	Unknown	No	Yes[3] (-2)	CGM 27%, SMBG 43% RD 16%, 95% CI -29% to -3% Conclusion: Statistically lower proportion of infants born to mothers in the CGM vs. SMBG group required admission to the NICU.	⊕⊕◯◯ LOW
Success (HbA1c ≤6.5%)	34 gestational weeks	1 (N=187) Feig 2017	No	Unknown	No	Yes[3] (-1)	CGM 66%, SMBG 52% RD 14%, 95% CI 0.2 to 28.1, adjusted p=0.06 Conclusion: No clear difference between groups after controlling for baseline values and mode of insulin delivery.	⊕⊕◯◯ LOW
HbA1c %: mean change from baseline	3, 5.25 and 8.25 months	1 (N=119) Secher 2013	No	Unknown	No	Yes[3] (-1)	**3 months:** MD 0.20, 95% CI -0.18 to 0.58 **5.25 months:** MD 0, 95% CI -0.38 to 0.38 **8.25 months:** MD 0.10, 95% CI -0.28 to 0.48 Conclusion: No statistical difference between CGM and SMBG at any timepoint.	⊕⊕◯◯ LOW
	6 to 6.75 months	2 (N=306) Feig 2017, Secher 2013	No	No	No	Yes[3] (-1)	Pooled MD -0.09, 95% CI -0.30 to 0.13, I^2 = 30%	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: No statistical difference between CGM and SMBG.	
	8.5 to 9 months	2 (N=306) Feig 2017, Secher 2013	No	No	No	Yes[3] (-1)	Pooled MD -0.15, 95% CI -0.32 to 0.01, I^2 = 0% Conclusion: No statistical difference between CGM and SMBG.	⊕⊕⊕◯ MODERATE
Hypoglycemia: % of SMBG values ≤70 mg/dl or % of time spent in the range <63 mg/dl	34 to 36 gestational weeks	2 (N=273) Feig 2017, Secher 2013	No	Unknown	Yes[4] (-1)	Yes[3] (-1)	% of SMBG values ≤70 mg/dl (1 trial, Secher) Median 14% (range 0% to 25%) for both CGM and SMBG groups, p=0.96; authors report that the women had a median of 4 (range 0-14) mild hypoglycemic events per week, with no difference between the groups (data not provided), but do not report events separately for type 1 and type 2 diabetes % of time <63 mg/dl, median (IQR) (1 trial, Feig) CGM 3% (1%-6%), SMBG 4% (2%−8%), p=0.10 Conclusion: No statistical difference between groups.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: CGM versus SMBG efficacy results in women with type 2 diabetes during pregnancy

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Pregnancy T2DM								
Gestational age and birth weight	up to 36 gestational weeks	1 (N=31) Secher 2013	No	Unknown	No	Yes[3] (-2)	CGM vs. SMBG, respectively (median, range): • *Gestational age*: 262 (206-280) vs. 267 (259-277) days, p=0.17 • *Birth weight*: 3,371 (1,070-4,260) vs. 3,343 (2,773-3,818) grams, p=0.70 Conclusion: No differences between groups. Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Proportion of infants large for gestational age	up to 36 gestational weeks	1 (N=31) Secher 2013	No	Unknown	No	Yes[3] (-2)	CGM 25% vs. SMBG 29% RD -1.7%, 95% CI -32.5% to 29.2% Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Neonatal hypoglycemia (2-hour plasma glucose <45 mg/dl) and **Severe Neonatal hypoglycemia** (2-hour plasma glucose <45 mg/dl treated with IV glucose infusion)	up to 36 gestational weeks	1 (N=28) Secher 2013	No	Unknown	No	Yes[3] (-2)	Neonatal hypoglycemia: CGM 31%, SMBG 14% RD 17.4%, 95% CI -13.0% to 47.9% Severe neonatal hypoglycemia: CGM 0%, SMBG 0% Conclusion: Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT
Miscarriage	up to 36 gestational weeks	1 (N=31) Secher 2013	No	Unknown	No	Yes[3] (-2)	CGM 0% vs. SMBG 7% RD -6.7% (95% CI -19.3% to 6.0%) Conclusion: One woman miscarried in the SMBG group compared with no women in the	⊕○○○ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							CGM group; insufficient evidence precludes drawing firm conclusions.	
Perinatal mortality	up to 36 gestational weeks	1 (N=31) Secher 2013	No	Unknown	No	Yes[3] (-2)	One case (3.2%, N=31) shortly after delivery due to severe shoulder dystocia. The authors did not report to which group the woman was randomized. <u>Conclusion</u>: Insufficient evidence precludes drawing firm conclusions.	⨁◯◯◯ INSUFFICIENT
Caesarean section rates	up to 36 gestational weeks	1 (N=31) Secher 2013	No	Unknown	No	Yes[3] (-2)	CGM 50% vs. SMBG 40% RD -10.0%, 95% CI -24.9% to 44.9% <u>Conclusion</u>: Insufficient evidence precludes drawing firm conclusions.	⨁◯◯◯ INSUFFICIENT
HbA1c % (Median)	8 to 36 gestational weeks	1 (N=30) Secher 2013	No	Unknown	No	Yes[3] (-1)	CGM vs. SMBG, respectively (median, range): • *8 weeks*: 6.4 (5.3-8.1 vs. 6.5 (5.3-9.0), p=0.56 • *12 weeks*: 6.2 (5.6-7.8) vs. 6.2 (5.1-7.7), 0.90 • *21 weeks*: 5.7 (5.2-6.9) vs. 5.6 (4.6-6.3), p=0.24 • *27 weeks*: 5.8 (5.0-7.7) vs. 5.7 (4.8-6.6), p=0.28 • *33 weeks*: 6.0 (5.1-7.0) vs. 5.9 (5.2-6.8), p=0.44 • *36 weeks*: 6.0 (5.1-6.5) vs. 5.9 (5.2-6.7), p=0.31 <u>Conclusion</u>: Insufficient evidence precludes drawing firm conclusions.	⨁◯◯◯ INSUFFICIENT
Hypoglycemia (% of SMBG values ≤70 mg/dl throughout pregnancy)	up to 36 gestational weeks	1 (N=30) Secher 2013	No	Unknown	Yes[4]	Yes[3] (-2)	CGM: median 5% (range 0%-19%) SMBG: median 4% (range 0%-15%) p=0.79 Authors report that the women had a median of 4 (range 0-14) mild hypoglycemic events per week, with no difference between the groups (data not provided), but do not report events separately for type 1 and type 2 diabetes	⨁◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: Insufficient evidence precludes drawing firm conclusions.	
Severe hypoglycemia (requiring second party intervention)	up to 36 gestational weeks	1 (N=30) Secher 2013	No	Unknown	No	Yes[3] (-2)	5 (17%) women experienced 15 severe hypoglycemic events, with no difference between the arms (data not provided). Conclusion: Insufficient evidence precludes drawing firm conclusions.	⨁◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
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4. Indirect, intermediate or surrogate outcomes may be downgraded.

Strength of Evidence Summary: CGM versus SMBG efficacy results in women with gestational diabetes

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Gestational diabetes								
Gestational age and birth weight	36 gestational weeks	1 (N=106) Wei 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	CGM vs. SMBG, respectively: • *Gestational age*: 37.5 ± 1.3 vs. 37.4 ± 0.1 weeks, p=0.92 • *Birth weight*: 3276 ± 520 versus 3451 ± 514 grams, p=0.08 Conclusion: No statistical difference between groups, though infants born to mothers in the CGM vs. SMBG group tended to weigh less.	⊕◯◯◯ INSUFFICIENT
Proportion of infants with macrosomia or large for gestational age	36 gestational weeks	1 (N=106) Wei 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	• *Macrosomia (birth weight >4000 g)*: CGM 8% vs. SMBG 13% RD -4.9%, 95% CI -16.4% to 6.6% • *Large for gestational age (≥90th percentile)*: CGM 35% vs. SMBG 53% RD -17.4%, 95% CI -36.0% to 1.2% • *Extremely large for gestational age (≥97.7th percentile)*: CGM 18% vs. SMBG 31% RD -13.3%, 95% CI -29.3% to 2.8% Conclusion: Infants born to women in the CGM vs. the SMBG group tended to be somewhat smaller, however there were no significant differences between groups on any measure.	⊕◯◯◯ INSUFFICIENT
Neonatal hypoglycemia	36 gestational weeks	1 (N=106) Wei 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	CGM 8% vs. SMBG 13% RD -4.9%, 95% CI -16.4% to 6.6% Conclusion: No statistical difference between groups.	⊕◯◯◯ INSUFFICIENT
Perinatal mortality	36 gestational weeks	1 (N=106) Wei 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	No perinatal deaths were observed in either the CGM or SMBG group.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: Insufficient evidence precludes drawing firm conclusions.	
Caesarean section rates	36 gestational weeks	1 (N=106) Wei 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	CGM 60% vs. SMBG 69% RD -8.3%, 95% CI -26.4% to 9.8% Conclusion: No statistical difference between groups.	⨁◯◯◯ INSUFFICIENT
HbA1c % (mean change from baseline)	32-36 gestational weeks	1 (N=106) Wei 2016	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	MD -1.0%, 95% CI -0.24% to 0.04% Conclusion: CGM group showed slightly lower levels vs. the SMBG group, but the difference between groups was not statistically significant.	⨁◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

5.2. Strength of Evidence Summary: Continuous Glucose Monitoring Safety and Adverse Events Results

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
Adverse events leading to discontinuation	3-6.5 months	8 (N=25 to 142) Battelino 2011, Deiss 2006, Hermanides 2011, O'Connell 2009, Tildesley 2013, Wei 2016, Lind 2017, van Beers 2016 2 observational (N=83 to 1714) 1 prospective cohort (Rachmiel 2015), 1 retrospective registry (Wong 2014)	No	Yes[2] (-1)	No	Yes[3] (-1)	Frequency in CGM arm across all RCTs was 0% to 24%. Older devices (6 trials): frequency 2% to 24%; the most common reasons for discontinuation included: • Difficulty operating the device and/or sensor (3% to 8%, 3 RCTs) • Alarms too frequent (6% in 2 RCTs) • Treatment discomfort or inconvenience; (20%, 1 small RCT, n=25) Newer devices (2 trials, N=52 to 142; Lind, van Beers): frequency, 1% to 4%; reasons for discontinuation were: • Allergic reaction to sensor (1%) • Could not upload CGM data (4%) Observational studies: Frequency much higher (61% and 44%) with similar reasons for stopping CGM use as were cited in the RCTs; however both studies were considered high risk of bias Conclusion: Discontinuation due to device-related adverse events was not uncommon in included studies. Most patients stopped CGM use due to difficulty operating the device or frequency of alarms (bothersome).	⊕⊕◯◯ LOW
	6 months	Flash CGM 2 (N=269) Bolinder 2016, Haak 2016	Yes[1] (-1)			Yes[3] (-1)	Frequency 2% to 5% across trials and included itching, rash, erythema, redness and weeping at the sensor insertion site; some events were unclear/not specified.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							Conclusion: Site-related AE discontinuation was not common; Reporting of adverse events was unclear.	
Serious device related adverse events (proportion with ≥1 event)	6-12 months	11 (N=14 to 244) Bergenstal 2010, Hermanides 2011, Hirsch 2008, Hommel 2014, JDRF 2008, JDRF 2009, Lind 2017, Maurus 2012, Tumminia 2015, Feig 2017, van Beers 2016	No	Yes[2] (-1)	No	Yes[3] (-2)	Frequency in CGM arm across all trials was 0% to 7%. Older CGM devices (9 trials): 0% to 7% and included: • Hospitalization for ketoacidosis (2% to 7%, 2 trials); *one case, 2% (1/44), was caused by pump failure.* • Serious skin reactions (0% to 6%, 2 trials) • Diabetes-related hospitalization (3%, 1 trial) • Insertion site infections resulting in cellulitis or skin abscess (1% each, 3 trials) • Serious device or study related adverse events not otherwise specified (0%, 2 trials) Excluding the trial with a very small sample size (n=14), the rate of serious device related adverse events was 0%-3%. Newer devices (2 trials, N=52 to 142, Lind, van Beers): % to 1%; the only serious device-related adverse event (as reported by authors) was Retinal detachment (1%) <u>Conclusion</u>: Serious device related adverse events (as reported by authors) were relatively rare across the trials. Sample size may be too small to detect rare outcomes.	⨁⨁◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	6 months	Flash CGM 2 (N=269) Bolinder 2016, Haak 2016	Yes[1] (-1)			Yes[3] (-1)	Frequency 1% to 3% included allergic reaction at sensor site, necrosis at sensor site, infection at sensor site and, rash, erythema, pain, and itching, Conclusion: Serious AEs appear to be rare, however severity is not defined and reporting of adverse events was unclear.	⊕◯◯◯ INSUFFICIENT
Non serious device-related adverse events (proportion with ≥1 event)	3 to 8.5 months	7 (N=25 to 157) Hermanides 2011, Lind 2017, New 2015, Yoo 2008, Tildesley 2013, Wei 2016, Feig 2017 1 prospective cohort (n=83) Rachmiel 2015	Yes[1] (-1)	No	No	Yes[3] (-1)	Frequency: 0% to 45% across all trials. Skin-related problems (e.g., erythema, inflammation, rash/allergic reaction, mild infection) at the sensor or insulin infusion site accounted for most of the events. Excluding the trial in women with preexisting type 1 DM during pregnancy (Feig) which reported 45% with skin changes (e.g. erythema, edema, scabbing, dry skin, hypo- and hyperpigmentation, other) the range across trials was 0% to 24%. Newer device (N= 142, Lind): 3% of patients experience skin-related problems, including allergic reaction to sensor, inflammation, itching, and rash at application site. The cohort study also reported that local skin reaction/irritation was common (36% of CGM patients) <u>Conclusion</u>: Non-serious device related adverse events, especially skin-related problems, are common with CGM use.	⊕⊕◯◯ LOW
	6 months	Flash CGM 2 (N=269)	Yes[1] (-1)			Yes[3] (-1)	Reported frequency of *events* 4% to 8% included allergic reaction at sensor site,	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
		Bolinder 2016, Haak 2016					rash, erythema, pain, and itching, edema, infection at sensor site. Trials also reported "expected sensor-insertion site *symptoms*" (not considered AEs by the authors), which occurred in 28% and 40% of subjects, and consisted of events similar to those reported as "non-serious device-related" events but provide no definitions or criteria to distinguish AE and symptom; it is unclear how these two outcomes differ and if there is overlap between them. Conclusion: Definitions of adverse events/distinction between events and symptoms was unclear, making it challenging to draw definitive conclusions	
Technical or mechanical issues	3 months	4 (N=27 to 157) Langeland 2012, Lind 2017, O'Connell 2009, Feig 2017	Yes[1] (-1)	No	No	Yes[3] (-1)	Frequency in CGM arms (3 trials):1% to 16%; issues, in 1 trial each, included: • Technical problems with sensor leading to loss of all glucose readings (15%) • Mechanical problems, not further specified (16%) • "Device issue" (1%) (newer CGM device; Lind) Women with preexisting type 1 DM during pregnancy (1 trial) n=103 CGM) using an older CGM device (Feig): • 81% complained of issues/frustration with the CGM device including: problems connecting transmitter to receiver, sensor not inserting properly, sensor pulling out accidentally, sensor stopped working early, sensor was	⊕⊕◯◯ LOW

Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
							uncomfortable, and other (not specified). • 78% did not use the device (assumed to have continued trial) for various reasons including alarms too frequent, inaccurate readings, too difficult to operate, sensor errors, calibration issues, other. **Conclusion:** Definitions and reporting of technical or mechanical issues varied and were not well reported across trials	

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

5.3. Strength of Evidence Summary: Differential Efficacy and Harms

Exposures	Outcome	Follow-up	RCTs	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	HTE-related	Conclusion	Quality
Baseline HbA1c; Age; Percent of CGM time <70 mg/dl; SMBG frequency; Education; Hypoglycemia Unawareness Score; Diabetes Numeracy Score; Hypoglycemia Fear Total Score; Type of clinical site (T1DM only)	Change from baseline in HbA1c %	6 months	**T1DM** 1 RCT (N=155) (Beck 2017)[a] **T2DM** 1 RCT (N=152) (Beck 2017[b])	No	Unknown	Yes[4] (-1)	Yes[3] (-1)	Yes (-1)[5]	**T1DM** No factors modified effect. **T2DM** Baseline Hypoglycemia Unawareness Survey scores: greater reduction in mean HbA1c % levels in subjects with **reduced awareness or uncertainty (score ≥3)**, vs. higher awareness (score ≤2), following **CGM** but not SMBG (interaction p=0.031). No other factors modified **Conclusion:** Insufficient evidence precludes drawing firm conclusions.	⊕○○○ INSUFFICIENT

Reasons for downgrading:

7. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
8. Inconsistency: differing estimates of effects across trials
9. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
10. Comparisons of an intervention to placebo or usual care is considered indirect.

The following apply specifically to heterogeneity of treatment effect (HTE):

11. Subgroup analysis not preplanned or unknown
12. Statistical test for homogeneity or interaction not performed

5.4. Strength of Evidence Summary: Cost-Effectiveness

Summary of cost-utility analyses comparing real-time CGM with SMBG in adults with type 1 diabetes

Type 1 Studies:	Chaugule 2017	Huang 2010	McQueen 2011	Roze 2014
Population	Adult only (avg. age = 46) Baseline HbA1c = 8.6% Type I Diabetes 53% Male MDI	Included two cohorts: Baseline HbA1c = 7.6 and 7.1%: for SMBG and CGM groups respectively with avg. age = 43 (25-73) 57% Female HbA1c <7.0% avg. age = 31 (8-65) Both MDI and CSII included	Adult only (avg. age 40) with Baseline HbA1c = 7.6% Type 1 Diabetes Assumed 20 yrs. since diagnosis Both MDI and CSII included	Adult only (avg. age =27) Baseline HbA1c = 8.6% 54.5% Female Assumed 13 yrs. since diagnosis CSII
Country	Canada	United States	United States	Sweden
Funding	Dexcom Inc.	JDRF Grant	Reports no funding received	Medtronic
Perspective	Canadian societal (Stated)	Societal	Societal	Swedish societal
Time horizon	50 years	Lifetime	33 years	70 years
Year/Currency	20161 USD = 1.3 CAD	2010 USD	2007 USD	2011 1 USD = 6.4 Swedish SEK
QHES	86/100	85/100	92/100	86/100
Results:				
ICER	$43,926/ QALY	$98,679 / QALY	$45,033 / QALY	$57,433 / QALY
One-way SA	Hypoglycemia disutility decrease by 50% caused ICER to increase to 84,972 Otherwise, results stable and within original CI: • Varying baseline HbA1c from 7.6 to 9.5 ICER remained between $43,848 and $45,215 • % HbA1c reduction CGM vs SMBG =0.3 and 0.9 were $45,159and $42,552	ICER increased to $701,397 if benefit restricted to lowering glucose. If daily costs of CGM reduced from $13.85 to $9.89 the ICER drops below $70,000 If 2 test strips used per day CGM would be cost saving	Utility of diabetes with no complications, the annual cost of CHD, and the probability of going from diabetes with no complications to the CHD disease state, had the largest impact on the model. The utility of diabetes with no complications was decreased (increased) by 50%, the ICER over $300,000 ($30,000) /QALY. Annual cost of CHD also had a large impact on the model results, and when decreased (increased) by 50%, the ICER was US$86,000 ($12,000) /	Increasing the CGM sensor use to 51 sensors/year $58,044 Varying the number of SMBG tests/day from 7.1, though 6.1, to 2.1 resulted in the ICER of $74,292, $68,183, $43,751 / QALY Altering the baseline HbA1c value from 8.6% to 7.2% to 9% changed the ICER to $92,759 $53,693 /QLY respectively Increasing the rate of severe

Type 1 Studies:	Chaugule 2017	Huang 2010	McQueen 2011	Roze 2014
			QALY. Results from Monte Carlo Probabilistic model CGM: $494,135 (420,381 - 571,631) QALY=10.812 (9.894 - 11.887) SMBG: $470,583 (397,782 - 550,598) QALY=10.289 (9.615 - 10.957) 48% of the Monte Carlo simulations were under US$50,000/QALY, while 70% were under US$100,000/QALY	hypoglycemic events reduced the ICER to $46,349 /QALY. Assuming no impact of fear hypoglycemia increased the ICER substantially (highest value reported; assuming a utility of 0.00552, decreased the ICER
Author's Conclusion	With a WTP threshold of $50,000 CGM was found to be a robustly, cost effective alternative to SMBG	Wide uncertainty with CI that included CGM dominating and being dominated by SMBG The immediate quality-of-life effect of CGM was responsible for the majority of projected lifetime benefits of the technology.	CGM was found to be cost effective in more circumstances than not, given a WTP of $100,000.	CGM is a cost–effective option in the treatment of Type 1 diabetes in Sweden
Limitations	• Canadian societal perspective stated but only direct costs reported • Sensitivity analyses related to long term impact of microvascular and macrovascular complications not presented • Model assumes lifetime horizon; RCT data provide information up to 12 months. Change in A1C based on DIAMOND trial; Unclear if 1% change with CGM use over lifetime is sustainable. • Industry funded	• Cardiovascular complications relied on type 2 diabetes cardiovascular models. • High baseline utilities effectively placed a ceiling on the potential quality-of-life benefit of CGM • Unclear if use of DCCT models for microvascular complications and type 1 DM models for cardiovascular complications reflect current care	• Some costs were extrapolated from studies that include all age groups. • RCT data provide information up to 12 months; sustainability of improved A1C unclear • Substantial variation in ICER estimates based on sensitivity analysis/modeling of diabetes complications based on probability evaluations from different populations	• Swedish societal perspective • Limited acknowledgment of modeling/study limitations • Model assumes lifetime horizon; RCT data provide information up to 12 months. • Industry ties

Summary of cost-utility analyses comparing real-time CGM with SMBG in adults with type 2 diabetes

Type 2 Studies:	Fonda 2016
Population	Adults avg. age= 57.8 years. Diagnosis with type 2 diabetes for at least 3 months. Not taking prandial insulin. Initial A1C of between 7% and 12% Both MDI and CSII
Country	USA (w/UK trial data)
Funding	Dexcom Grant
Perspective	Third-party payer (direct costs only)
Time horizon	Lifetime
Year/Currency	2011 USD
Discounting	3%
Cost sources	Provided by Dexcom Inc. and published literature[2,102,117,151]
QHES	75/100
Results:	
ICER	$8,898 / QALY
One-way SA	Results not discussed
Other SA	Probabilistic cost-effectiveness analysis suggests that the likelihood of the intervention being cost-effective is 70% at the willingness-to-pay threshold of $100,000 per QALY.
Author's Conclusion	CGM offers a cost-effective alternative to populations matching that the trial specifically: short-term, intermittent use in people with type 2 diabetes.
Limitations	• Small sample size of trial (n = 100) to estimate effectiveness parameters. • Limited sensitivity analyses presented. • Used older CGM device that has since been update. • Life-time horizon used; Few RCT data past available on long-term CGM use in type 2 DM. • Unclear if use of DCCT, USPKD and Framingham data for complications reflect current care

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