

WASHINGTON STATE HEALTH CARE AUTHORITY

# Public Comments and Responses

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Health Technology Assessment

Tuesday, February 14, 2012

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## Health Technology Assessment Program

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<http://www.hta.hca.wa.gov>

# On- and off-label uses of rhBMP-2 or rhBMP-7 for spinal fusion

Provided by:



**Spectrum Research, Inc.**

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**Responses to public comments and clinical reviews**

February 14, 2012

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## Response to comments from Washington State's Department of Labor and Industries

### Technical Edit:

- Page 12 "publication exclusion, 4th bullet" reference is in error. The report should have a careful general edit for any others.
  - *Response:* The referenced error has been corrected and the report has undergone an additional general edit to check for errors.

### General Concerns:

- One of the most important issues of context for the policy decisions the clinical committee must make includes differentiating when findings reported as significant have meaningful clinical differences. This is especially important when interventions have potential safety concerns. This issue seems to have been minimized in the summary presentation especially. There has been substantial discussion in the literature about interpretation of change scores in back conditions that might help frame this context better (eg, Ostello et al. Interpreting change scores for pain & functional status in low back pain. Spine 2008; 33:90-94. ; Carragee et al. Minimal acceptable outcomes after lumbar spine fusion Spine J 2010; 10:313-320.)
  - *Response:* We agree with this comment and have updated the report so that one can better differentiate whether reported findings have meaningful clinical differences. We used what seemed to be appropriate MCID values based on the results in Key Question 1.
- Given the substantial amount of critique and discussion in the literature regarding these studies, it seems appropriate for there to be a more robust discussion in the report to clarify strength and level of evidence along with deficiencies and limitations of the studies.
  - *Response:* The strength and level of evidence have been stated more consistently throughout the report. Deficiencies of the RCTs are stated clearly in the results section when discussing the studies. Deficiencies of the cohort studies are reflected in the LoE grade; further details are given in the appendices.

### Executive Summary and Summary Evidence Tables:

- A contextual summary is not included to frame the lengthy study summary in the executive summary. A contextual summary would include expected outcome, theoretical benefits and drawbacks, overall evidence (e.g. numbers of studies for safety, efficacy, effectiveness) and SoE.
  - *Response:* We have added additional information to the Executive Summary to provide more context on expected outcome, theoretical benefits and drawbacks, overall evidence, and SoE.

- Primary outcomes versus outcomes studied/reported in trial are not clearly identified. This would be clarified (perhaps most easily in the summary tables).
  - Response: We have added additional information to the Executive Summary and to provide more context on the above.
- Consistency is needed in text description of studies (some include N (helpful), others do not; some indicate LoE rating, others do not - in the summary, without referencing later material, the IIA is not very meaningful). The summary statement should indicate what level of overall evidence (SOE) for each section, at least where conclusions are indicated, but would be helpful for overall consistency to have in each section.
  - Response: We agree; we have updated the summary statements to reflect these changes. We have left the RCT LoE ratings as they are graded, ie., as IIA or IIB, in order to maintain consistency of these grades throughout the report.
- Consider separating and moving the relevant summary tables for studies impacting key questions under each text summary of the key questions. This would help improve the readability and consistency of information for the committee.
  - Response: We have added additional information to the summaries and the summary tables so that each can be read independently of one another. This should aid in readability of the information for the committee.
- Related to the general concern above, there is inconsistent usage of significance – it is unclear if statistical significance or MCID is being reported as significant. If significance is noted, a reference to whether this could be considered MCID or not should be noted.
  - Response: We agree and have updated the summaries and text to address this concern, as noted above.
- Regarding safety: usage of "low" rates of events is not defined - either use the actual range or define and reference expected rates when using a term such as "low."
  - Response: We agree and have changed the language to avoid confusion.
- On the Summary table, some headers (see KQ2) appear missing.
  - Response: This has been corrected.
- Consider consistently including "n" in trial descriptions in the tables.
  - Response: This information has been added.

### **Response to letter from Clyde Carpenter, MD**

- We appreciate your comments. They will be available to the HTCC.

### **Response to letter from Ryan Halpin, MD**

- Background: Clarification requested regarding retrograde ejaculation for ALIF.
  - *Response: Description of ALIF modified to clarify risk.*
- We appreciate your comments. They will be available to the HTCC.

### **Response to letter from Doug King (Medtronic) (Jan. 18, 2012)**

- We appreciate your comments. A response has been made by the Washington State Health Care Authority.

### **Response to letter from Doug King (Medtronic) (Jan. 30, 2012)**

- Medtronic recognizes the value of the HTA on BMP and appreciates the thoroughness of the report. In particular, Medtronic agrees with the inclusion of descriptions of the various surgical approaches and instrumentations to achieve spinal fusion in Section 2.6, as it makes the distinction between on-label and off-label use of BMP clear. Moreover, these variables affect the effectiveness of rhBMP-2 use and are thus important to explain. Different surgical approaches are often necessary depending on the anatomical considerations and the need for focal or extensive decompression the options for reduction and stabilization techniques, as well as individual patient issues impacting potential surgical risks of a particular procedure. ... Furthermore, Medtronic commends the incorporation of donor site morbidity associated with ICBG harvesting. Based on our experience with rhBMP-2, we believe the evidence review will be more clinically useful and accurate if the researchers clarify a number of elements contained in the draft report. As such, we submit the following comments.

#### **General recommendations**

- Defer finalizing the review until after the release of the Yale findings in Fall 2010.
  - *Response: A response has been made by the Washington State Health Care Authority.*
- Explain the distinction b/w InFUSE and AMPLIFY in the introduction. We note the specific reference to InFUSE in the key questions and would like to alert the reviewers

that the research results at times conflate the use of InFUSE with data on AMPLIFY, a product that is not commercially available in the US at this time. Medtronic is in the process of seeking FDA's approval to market this new bone graft product for single-level, posterolateral spinal fusion procedures in patients with DDD. AMPLIFY's concentration and dosage of rhBMP-2, as well as its carrier composition, are substantially different from InFUSE, which has been available commercially since 2002. Please see Fig 1 in the appendix for more information on the differences between InFUSE and AMPLIFY. In order to ensure the distinction b/w InFUSE and AMPLIFY is clear in the report, we recommend that the researchers explain the distinction in the introduction and clearly identify studies that evaluate and those that evaluate InFUSE. Similar, the report also references evidence of another investigational formulation- BCP/rhBMP-2 throughout the report.

- *Response:* We have added information on AMPLIFY and how it differs from InFUSE in the introduction.

### Methods section

- Clarify the methodology used to identify the evidence base for the key questions. In Figure 1, the flow chart showing results of the literature search, there are several citations that are unaccounted for after the application of the inclusion and exclusion criteria from the total number of citations. While Medtronic recognizes the complexities associated with the literature search, such as studies meeting more than one inclusion criteria, Medtronic requests clarification on the numbers of studies in the flow chart showing results of the literature search to ensure each study considered is appropriately and clearly accounted for.
  - *Response:* We have identified and corrected the errors in Figure 1 in the draft report.
- Ensure appropriate and consistent use of reference numbers for each finding throughout the report. As an example, reference numbers are missing on page 18 and 19 under the summary paragraphs for overgrowth and uncontrolled bone formation and osteoclast activity, whereas the references are included in the next paragraph on wound infections.
  - *Response:* We have updated the report and provided previously missing reference numbers as appropriate.
- Based on the AHRQ's framework for best practices in systematic review, Medtronic recommends the removal of Carragee (2011) (review) as a classification of a systematic review on page 67, Table 4.

- *Response:* As the referenced article is a systematic review, it is appropriate to keep it in this Table, which provides an overview of the evidence base and conclusions made by previously conducted systematic reviews.
- Remove details of study sponsorship and consulting fees from the evidence tables, as they are not relevant to the research questions in this report. Additionally, these fees were not systematically reported for any other manufacturer of BMP without any explanation.
  - The HCA requests that study sponsorship information be included in the report. We included such information for all studies included in KQ2 (efficacy/effectiveness). In order to do this, we include information on funding source as reported by each study. Any additional information we identified was reported in the form of footnotes (all such information was identified in the Carragee 2011 peer-reviewed critical review).

### Key question 2

- Request inclusion of Burkus (2009) in the final report's evaluation of efficacy and effectiveness of rhBMP-2 use in on-label lumbar fusion.
  - *Response:* We accepted the search and inclusion/exclusion of studies done by the AHRQ HTA on BMP (2010) for the efficacy and effectiveness section. The cited Burkus 2009 study was excluded by the AHRQ HTA for the following reason: “postmarketing follow-up, large dropout”.

### Key question 3

- Include a robust discussion on whether the adverse events identified are clinically meaningful. Though the WA HTA completed a comprehensive assessment of a wide range of adverse events, the HTA does not provide adequate context as to whether all of the endpoints are clinically meaningful. As an example on page 188 under rhBMP-2 off-label use, lumbar spine, the HTA only briefly explains there was no evidence that the occurrence of heterotopic bone formation and/or elevated antibody responses to BMPs impacts actual patient outcomes. This is an important point that deserves more of a discussion in the report so that these rates are accurately interpreted. ... Medtronic recommends for the WA HTA to provide a robust discussion as to whether all of the adverse events are clinically meaningful, as we believe that the link is equally as important as the thoroughness on the range of events.
  - *Response:* An attempt has been made to provide information as to whether adverse events are clinically meaningful.



- Request inclusion of Burkus (2011) in the final report's evaluation of the incidence of rhBMP-2 antibody formation in lumbar spine applications.
  - *Response:* As noted by Medtronic, this study was published after the literature search period and thus was not considered for inclusion.

### Key question 5

- Exclude Garrison (2007) from the WA HTA, given the potential differences in healthcare systems, treatment practices and costs between the US and UK.
  - *Response:* This study meets our inclusion criteria. It has been made clear that the Garrison study was conducted in the UK setting.

### Response to clinical review from Dr. Michael Jihoon Lee, M.D.

- Background: There are several inaccuracies regarding the definition of various fusion subtypes.
  - *Response:* Inaccuracies in the Background section regarding definitions of DDD and various surgical procedures have been corrected.
- Methods: The implications of the major findings are not clearly stated. The draft is like a very exhaustive book report, but in the end it is not clear what the recommendations are. Perhaps that was the intent and the reader can draw their own conclusions. But I get the sense that the authors preferred to put the information out there without putting together a recommendation or even an implication in the end. Personally, I am okay with that.
  - *Response:* Conclusions for each outcome have been added to the report in the summary paragraphs.
- Methods: One of the issues that has been raised recently is the possibility of conflict of interests in reporting. Many of the authors cited are or were paid consultants for Medtronic and while this relationship does not necessarily negate their findings, it is worthwhile noting that concern has been raised in the literature regarding these relationships. It would be a lot of work, but it would be nice if there were an easy way to identify a study that had a potentially conflicted author or was industry studied. It was done at many points in the draft but it did not appear consistently.
  - *Response:* This information was provided for comparative studies included in KQ2; additional information for studies included only in KQ3 is available in the detailed appendix tables.
- Overall presentation and relevancy: The information is clearly presented but the conclusions seem to be lacking.

- *Response:* Conclusions for each outcome have been added to the report in the summary paragraphs.
- Quality of report: Overall this is a superior report. I would alter the definition of various kinds of fusion as they are not accurate in their present form. I would consider discussing potential conflicts of interest of authors cited and emphasize that this draft is a review of all available literature. I don't know if a conclusion section is lacking or if it was intentionally not included so the reader may draw their own conclusions.
  - *Response:* Thank you. The definitions of fusion have been corrected. Conclusions for each outcome have been added to the report in the summary paragraphs.

#### **Response to clinical review from Dr. Brian Drew, M.D.**

- Background: There are several inaccuracies in the surgical procedures section (details provided).
  - *Response:* Some of these inaccuracies had already been corrected based on comments from another reviewer. Remaining inaccuracies have been corrected.
- Conclusions: There were a variety of conclusions reached in this report. I believe that based on the current literature the conclusions of this review are valid. After reviewing the report a noted issue that was not mentioned was the issue of the accuracy of determining whether a spine is fused. This is the primary issue with the use of rhBMP. It is used with the belief that it will provide a better, or at least as reliable of a fusion, as iliac crest bone graft. To determine if a spine is fused or not requires some form of radiographic evaluation. Generally X-rays or CT scans are used. There is not a standard agreed upon method to evaluate the success of a complete spine fusion in the literature. The literature varies significantly on what radiographic criteria they use to determine if a spine is fused or not. More importantly it is not known how accurate or valid X-ray or CT scans are in determining whether a spine is fused or not. In the overall context of this report and considering the numerous outcome measures used in this report this is still a small but clinically important flaw when comparing fusion studies. I am not aware of a current solution to this problem but I thought it would be important enough to mention in the radiographic outcome conclusions.
  - *Response:* Changes were made in Section 4.1, KQ1 Treatment Outcomes, to address and discuss this issue.



### HTA Program Responses to comments on Draft BMP Data

Comment	Program Response
<p>In Figure 1a on page 44, there is a 4-year total of 1,345 spine fusion cases in the Public Employee Benefits (PEB) group. However, the sum of the spine fusion cases reported across the four year period in the table is 1,386.</p>	<p>The figure (now 2a) is amended with a footnote indicating that this is a count of unique patients over 4 years.</p>
<p>In comparing Figures 1b and 2b, there is a discrepancy in the numbers for L&amp;I. In Figure 1b, the L&amp;I 4 year total reported was 2813 spine fusion cases; however, the sum of the cases reported across the 4 year period in the table is 2961. If this is not a simple reporting error, we would appreciate clarification on the discrepancy.</p>	<p>The Figures in question (now 2b and 3b) have been reviewed for consistency between agencies in reporting hospital inpatient fusions. The total patients on Figure 2b for 4 years are 2479, while the total patients adding the 4 years of figure 3b are 2658. These counts differ because the total in 2b is a count of unique patients over 4 years. A footnote has been added to clarify this.</p>
<p>When reviewing data from figures 3a and 3b, there are approximately 500 cases missing based on the number of cases reported in Figures 1a and 1b.</p>	<p>The figures in question (now 4a and 4b comparing to 2a and 2b) appear to have been consistent between 2a and 4a with 160 cases reported in both. However, we found that an incorrect table was inserted for Figure 4b. Figure 4b is replaced with the correct table.</p>
<p>The data tables by MS-DRG show 0 total spine fusion cases in 2009 for MS-DRG 459 and 1 in 2010. However, in similar tables showing cases with BMP, there is 1 BMP case assigned to MS-DRG 459 in 2009 and 2 BMP cases assigned to that MS-DRG in 2010. It is unclear why there were more BMP fusions in these MS-DRGs each year than there were total fusions cases in that DRG</p>	<p>The Figures in question (now 4a and 4b) showed the number of fusions reporting BMP use correctly as 160 cases. However, we found that an incorrect table was inserted for Figure 4b. Figure 4b has been replaced with the correct table.</p>

**Clinical review #1: Dr. Michael Jihoon Lee**

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for hip resurfacing. Your contribution and time are greatly appreciated.

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

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to [joe@specri.com](mailto:joe@specri.com)

If you have questions or concerns please contact Joseph Dettori, PhD at the email above.

**Reviewer Identification Information**

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**INTRODUCTION Comments**

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

- Overview of topic is adequate? **YES**

- Topic of assessment is important to address? **YES**
- Public policy and clinical relevance are well defined? **YES**

## BACKGROUND Comments

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

- Content of literature review/background is sufficient? **No, there are several inaccuracies regarding the definition of various fusion subtypes. I have tried to clarify them in the text below:**

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**Page 42      First  
                  paragraph**

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The paragraph describing DDD as the “most common cause of back pain” is not accurate. If anything, DDD as a cause of a back pain is quite controversial. I would recommend softening up the language as something like, “DDD has been extensively discussed as an etiology for back pain.” Instead of “Pain occurs in the back and legs..”, you might consider “Pain can occur in the back and legs...” Similarly, the “arthritic facets MAY be a source of pain.” The language surrounding DDD is too strong in my opinion and should be softened so physicians who do not believe that DDD is a legitimate source of pain would not object.

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**Page 42      ALLOGraft  
                  t  
                  paragraph**

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I would suggest altering the statement of allograft being “osteoconductive and weakly osteoinductive” to “Allograft is osteoconductive and MAY be osteoinductive.”

Page 45, Paragraph on PLF. *“PLF places the graft between and cage between the transverse processes and secures with pedicle screws or rods.”* This is not accurate. PLF entails placement of bone graft in the posterior lateral gutters between the transvers process of the level above and the level below. It does NOT entail the use of instrumentation. PLF can be performed with or without instrumentation. Furthermore, there is NO cage with PLF.

*“However, it does not limit the movement in the disc space as well as the other approaches.”* There is insufficient evidence to support this statement, I would eliminate it altogether.

Page 45 paragraph on PLIF. *“Both a laminectomy and facetectomy are performed to create a large disc space for the bone graft material and threaded interbody fusion cage.”* This is not quite accurate. I would suggest *“A laminotomy and partial facetectomy are performed to access the disc space for discectomy and bone graft and possible cage placement.”* The PLIF does not require a threaded cage or even a cage at all. *“By fusing the degenerative vertebrae, the unstable spinal motion characteristic of DDD ceases and provides relief<sup>16</sup>.”* I would alter this to *“By fusing the degenerative vertebrae, the motion pathology is eliminated and can cause pain relief.”* *“A bilateral laminotomy is then performed and with the inferior articular face exposed, bone is removed from the disc space.”* DISC is removed from the disc space, not BONE. *“The threaded interbody fusion cage is then fixed with pedicle screws and stabilized with rods<sup>84</sup>.”* This is not accurate. I would suggest *“Pedicle screw fixation with rods are often used to provide supplemental fixation.”*

Page 45 on TLIF: *“Transforaminal lumbar interbody fusion (TLIF) is similar to PLIF in method and instrumentation; however, the approach is posterolateral as opposed to purely posterior. A threaded interbody fusion cage is used, with or without pedicle screws.”* This is not quite accurate, but close. TLIF is similar to PLIF. The approach is slightly more lateral as a complete facetectomy is generally done in a TLIF whereas a partial facetectomy is generally done in a PLIF. Both PLIF and TLIF do not require a threaded cage. They both entail the placement of bone graft into the disc space with or without a cage.

Page 45 on ALIF: an ALIF entails that removal of disc material utilizing an anterior approach, followed by the placement of bone graft in the disc space (with or without a cage). It does not entail pedicle screw fixation.

Page 45 on Autogenous Bone Grafting: *“The grafts, in the form of chips or strips are then covered with marrow blood”.* I would change this to *“Bone graft may be harvested as a weight bearing strut or as morselized cortical and cancellous bone.”*

## REPORT OBJECTIVES & KEY QUESTIONS Comments

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

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

## METHODS Comments

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

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

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

- Amount of detail presented in the results section appropriate? **YES**
- Key questions are answered? **YES**
- Figures, tables and appendices clear and easy to read? **YES, but there were so many.....**
- Implications of the major findings clearly stated? **NO. The draft is like a very exhaustive book report, but in the end it is not clear what the recommendations are. Perhaps that was the intent and the reader can draw their own conclusions. But I get the sense that the authors preferred to put the information out there without putting together a recommendation or even an implication in the end. Personally, I am okay with that.**
- Recommendations address limitations of literature? **One of the issues that has been raised recently is the possibility of conflict of interests in reporting. Many of the authors cited are or were paid consultants for Medtronic and while this relationship does not necessarily negate their findings, it is worthwhile noting that concern has been raised in the literature regarding these relationship. It would a lot of work, but it would be nice if there were an easy way to identify a study that had a potentially conflicted author or was industry studied. It was done at many points in the draft, but it did not appear consistently so...**



**CONCLUSIONS Comments**

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

- Are the conclusions reached valid? **I didn't see a Conclusions section?**

**OVERALL PRESENTATION and RELEVANCY Comments**

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

- Is the review well structured and organized? **YES**
- Are the main points clearly presented? **The information is clearly presented, but the conclusions seem to be lacking?**
- Is it relevant to clinical medicine? **YES**
- Is it important for public policy or public health? **YES**

**QUALITY OF REPORT**

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**Quality Of the Report**

(Click in the gray box to make your selection)

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Superior  Sup

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**Overall, this is a superior report. I would alter the definition of the various kinds of fusion as they are not accurate in their present form. I would consider**

**discussing potential conflicts of interest of authors cited and emphasize that this draft is a review of all available literature. I don't know if a conclusion section is lacking, or if it was intentionally not included so the reader may draw their own conclusions. Anyone who spends the time to read it ought to come up with their own conclusions, but it will take a long time to read and go through. This is an outstanding report and it took me a long time to read it, so I can only imagine how long it took to compose.**

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We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

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Not usable. Preferred to "free hand" everything.

**Clinical review #2: Dr. Brian Drew**

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

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**Reviewer Identification Information**

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## REPORT OBJECTIVES & KEY QUESTIONS Comments

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

## METHODS Comments

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

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

- Amount of detail presented in the results section appropriate? **YES**
- Key questions are answered? **YES**
- Figures, tables and appendices clear and easy to read? **YES, but there were so many.....**
- Implications of the major findings clearly stated? **NO. The draft is like a very exhaustive book report, but in the end it is not clear what the recommendations are. Perhaps that was the intent and the reader can draw their own conclusions. But I get the sense that the authors preferred to put the information out there without putting together a recommendation or even an implication in the end. Personally, I am okay with that.**
- Recommendations address limitations of literature? **One of the issues that has been raised recently is the possibility of conflict of interests in reporting. Many of the authors cited are or were paid consultants for Medtronic and while this relationship does not necessarily negate their findings, it is worthwhile noting that concern has been raised in the literature regarding these relationship. It would a lot of work, but it would be nice if there were an easy way to identify a study that had a potentially conflicted author or was industry studied. It was done at many points in the draft, but it did not appear consistently so...**

**CONCLUSIONS Comments**

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

- Are the conclusions reached valid? **I didn't see a Conclusions section?**

**OVERALL PRESENTATION and RELEVANCY Comments**

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

- Is the review well structured and organized? **YES**
- Are the main points clearly presented? **The information is clearly presented, but the conclusions seem to be lacking?**
- Is it relevant to clinical medicine? **YES**
- Is it important for public policy or public health? **YES**

**QUALITY OF REPORT**

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**Quality Of the Report**

(Click in the gray box to make your selection)

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Superior  Sup

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**Overall, this is a superior report. I would alter the definition of the various kinds of fusion as they are not accurate in their present form. I would consider**

**discussing potential conflicts of interest of authors cited and emphasize that this draft is a review of all available literature. I don't know if a conclusion section is lacking, or if it was intentionally not included so the reader may draw their own conclusions. Anyone who spends the time to read it ought to come up with their own conclusions, but it will take a long time to read and go through. This is an outstanding report and it took me a long time to read it, so I can only imagine how long it took to compose.**

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We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

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Not usable. Preferred to "free hand" everything.