Response to the reviewer’s comments

Many thanks for the extremely useful comments and positive feedback. Please find below my response to each comment.

Reviewer 1

1. The Introduction could be improved by adding a couple of sentences explaining why adverse effects of medical devices might be an important healthcare topic.

Response: Thank you. We agree completely and have added the following text in the introduction:

“In particular, the importance of the adverse effects of medical devices has been highlighted recently in the press by articles on the potential harm from breast implants and hip prostheses. Although the regulatory process for medical devices is less stringent than for pharmaceutical interventions, the adverse effects of medical devices can be just as serious and can be an important factor in decision-making for health professionals, policy makers and patients. Identifying the evidence on adverse effects for medical devices is, therefore, paramount to inform healthcare decisions.”

2. Methods - perhaps a brief clarification to say that studies were identified through searching for intervention and disease condition (spinal fusion), and no adverse effects terms were used. However, this may miss adverse effects of the intervention when used in other bone conditions, or when the spinal fusion was not mentioned.

Response: Thank you. We agree and I have added the following text in the methods:

“No adverse effects terms were applied to the search strategy in order to try to maximise sensitivity and allow a prospective analysis of the potential performance of adverse effects terms if they had been included. A pragmatic decision was made to include disease terms (spinal fusion) although it was appreciated that this may have missed papers which referred to adverse effects...
of the intervention in other bone conditions, or where spinal fusion was not mentioned. No study design or date limits were applied and the full search strategy is published elsewhere (6, 7).

3. Adverse effects terms - I have some difficulty judging the item 2. which relates to specific adverse events such as swelling, dysphagia etc. Why would anyone key in such search terms for a bone product in spinal fusion? Were these terms mentioned in the manufacturer's product information, or are well-recognized in association with this product? I think there is a major caveat here in that use of specific terms is well and good if the searchers have a clear idea beforehand what are the key events, but it is not helpful for unexpected or new events.

Response: Thank you. We agree and I have added the following text in the methods;

“This review was undertaken after a number of sources raised concerns about the safety of rhBMP-2: during the post-marketing period several non-industry observational studies reported adverse events possibly associated with the use of rhBMP-2; the Food and Drug Administration (FDA) issued a public health notification of potentially life-threatening complications associated with swelling of neck and throat tissue after rhBMP-2 use in the cervical spine; and a subsequent review of publicly available data suggested an increased risk of complications and adverse events for patients receiving rhBMP-2 that was 10 to 50 times higher than the original randomised controlled trial (RCT) estimates. These sources identified a number of specific adverse events of concern - some dependent upon spinal location - such as dysphagia, retrograde ejaculation, heterotopic bone formation, and osteolysis.”

And we have added this text to the limitations;

“The usefulness of searching with specific terms is measured here but this will only be applicable to those reviews in which the searchers have a clear idea beforehand what the potential key events are. This approach is not as useful for unexpected or new events. However, in this case study review we have also demonstrated the value of generic adverse effects terms which can be used in any review.”

4. The Discussion should point out limitations such as the fact that this product is rather atypical for a device in that it has a pharmaceutical component. Thus the findings may be less generalizable.

Response: Thank you. We agree and I have added the following text in the limitations;

“The medical device is also rather atypical for a device in that it has a pharmaceutical component. Thus our findings may be less generalizable.”

Reviewer 2

1. Inaccurate citation for Citation #5 - Poster Presentation by CADTH authors. See:

Farrah K, Mierzwinski-Urban M, Cimon K. Playing it safe: validating search filters for adverse events. Poster presented at: 2013 Annual Meeting and Exhibition of
the Medical Library Association (MLA ’13), the 11th International Congress on Medical Librarianship (ICML), the 7th International Conference of Animal Health Information Specialists (ICAHIS), and the 6th International Clinical Librarian Conference (ICLC). One Health: Information in an Interdependent World; 2013 May 3-8; Boston, MA
http://www.cadth.ca/media/is/MLA-Poster_Kelly.pdf

Response: Many thanks for pointing this out. This has been corrected.

2. Minor typo in abstract - Emabse should be Embase
Response: Again many thanks for pointing this out. This has been corrected.

Discretionary Revisions:

1. Consider providing a quality rating of the selected systematic review using e.g., AMSTAR - as testimony to its high quality.
Response: Thank you for your suggestion. We have carefully considered this but feel that as the authors of the systematic review we may not be best placed to assess its quality. We hope as this was a discretionary revision that this is agreeable with the reviewer.

2. Consider providing more explanation as to why only two facets/concepts were used in case study systematic review search - this is alluded to elsewhere but perhaps indicate that no research design filters or any limitations were placed on the search (and why)
Response: Thank you. We agree and I have added the following text in the methods;

“No adverse effects terms were applied to the search strategy in order to try to maximise sensitivity and allow a prospective analysis of the potential performance of adverse effects terms if they had been included. A pragmatic decision was made to include disease terms (spinal fusion) although it was appreciated that this may have missed papers which referred to adverse effects of the intervention in other bone conditions, or where spinal fusion was not mentioned. No study design or date limits were applied and the full search strategy is published elsewhere (6, 7).”

3. Consider incorporating "feasibility study" as part of the title
Response: Thank you. We have incorporated this useful suggestion in the title.