

## *Comparative Effectiveness Review Disposition of Comments Report*

### **Research Review Title:** *Management of Postpartum Hemorrhage*

Draft review available for public comment from November 21, 2014 to December 17, 2014.

**Research Review Citation:** Likis FE, Sathe NA, Morgans AK, Hartmann KE, Young JL, Carlson-Bremer D, Schorn M, Surawicz T, Andrews J. Management of Postpartum Hemorrhage. Comparative Effectiveness Review No. 151. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2012-00009-I.) AHRQ Publication No. 15-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2015.  
[www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

### **Comments to Research Review**

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

| Commentator & Affiliation | Section               | Comment   | Response  |
|---------------------------|-----------------------|---|---|
| <b>TEP Reviewer #1</b>    | Clarity and Usability | This report is precise and eloquent The organization is superb The underscoring of the limitations of the state of the art of obstetrical hemorrhage will serve to motivate those reading this document to begin to fill in the gaps. | Thank you for your comment.   |
| <b>Key Informant #1</b>   | Clarity and Usability | The report is well structured and presents a clear picture of past research.  | Thank you for your comment.   |
| <b>Key Informant #1</b>   | Clarity and Usability | The report identifies the need for a call to action for good quality research related to interventions and management of PPH  | Thank you for your comment.   |
| <b>Key Informant #1</b>   | Clarity and Usability | There are no implications for practice from this report but a need for further evaluation and precise identification of procedure.  | Thank you for your comment. We attempted to point out implications inherent in even this limited literature in the Discussion.  |
| <b>TEP Reviewer #2</b>    | Clarity and Usability | See comment number 1 above  | Thank you for your comment.   |
| <b>TEP Reviewer #3</b>    | Clarity and Usability | The report is well organized but will not be able to translate into policy or practice decisions.   | We agree that the evidence base is limited but have attempted to stress findings that can inform practice decisions.  |
| <b>Peer reviewer #1</b>   | Clarity and Usability | The report is very well structured and clear. The main points are clearly presented. The conclusions can be used to inform future research.   | Thank you for your comment.   |
| <b>Peer reviewer #1</b>   | Clarity and Usability | I wonder if it would be worthwhile to recommend that federal funding be targeted (through RFAs and the like) to encourage research that will improve the evidence base for this common obstetrical complication.                      | We have noted the need for additional studies in the Research Gaps section of the report and hope that the report will be used to inform policy, funding, and practice decisions. |
| <b>Peer Reviewer #2</b>   | Clarity and Usability | Yes   | Thank you for your comment.   |

| Commentator & Affiliation | Section               | Comment  | Response   |
|---------------------------|-----------------------|--|--|
| <b>TEP Reviewer #4</b>    | Clarity and Usability | Structure of the report is excellent with the following exception. The executive summary is very heavy on use of abbreviations. This makes it hard to follow. Suggest removing all nonstandard and nonessential abbreviations from the summary (eg TXA, SOE) for readability. (This was not such a problem in the body of the report).   | We have eliminated non-standard abbreviations in the Executive Summary.                              |
| <b>Peer reviewer #3</b>   | Clarity/Usability     | Overall well-done.   | Thank you for your comments.   |
| <b>TEP Reviewer #1</b>    | General               | Overall the manuscript is well written and highly detailed. There are only a few syntax errors   | Thank you for your comment. We have revised the document and hope that we have corrected any errors. |
| <b>TEP Reviewer #1</b>    | General               | Maternal hemorrhage is a significant public health emergency. Although the obstetrical community is aware of its importance, we are unaware of the weaknesses that plague the evidence that drives our clinical protocols. This analysis highlights the difficulties of evaluating possible complications from the proposed interventions in our algorithms and the almost impossible task of dealing with confounding by indication | Thank you for your comment.  |
| <b>TEP Reviewer #1</b>    | General               | Table B line 58 in findings column ends abruptly   | This row in the table ends on the next page in the PDF version sent for review (line 3 page 59).     |
| <b>Key Informant #1</b>   | General               | Clinically relevant topic, poorly studied and reported in the US.  | Thank you for your comment.  |
| <b>Key Informant #1</b>   | General               | The population and audience are clearly defined.   | Thank you for your comment.  |
| <b>Key Informant #1</b>   | General               | The key questions are appropriate  | Thank you for your comment.  |

| Commentator & Affiliation | Section | Comment   | Response   |
|---------------------------|---------|---|--|
| TEP Reviewer #2           | General | This was a very long publication with segments that appear to be repetitive (but, of course, are not). The reviewers' job was made very difficult by poor organization/display of the table of contents, which do not make clear that the executive summary pages are numbered separately from the rest of document.  | The report follows AHRQ standards for the table of contents, and we hope that our revisions throughout the document help to improve readability.   |
| TEP Reviewer #2           | General | Our job as reviewers was also hampered by the different page numbering placed by the Scholar One system. I would recommend that AHRQ reassess the organization of these documents so that reviewers do not have to struggle. This may be done simply by making the table of contents more specific. My comments below use the page and line numbers placed by the Scholar One system because they are unique to each page and will not create confusion about the part of the document to which I am referring with any individual comment.   | Thank you for your comment.  |
| TEP Reviewer #2           | General | Figure A, the analytic framework, is excellent and critical to understanding the rest of the document. This should remain in each place where it is seen  | Thank you for your comment.  |
| TEP Reviewer #2           | General | Page 28 line 58 to page 29 line 4 and Page 130 line 11. Conclusions. The authors state: "Few studies addressed pharmacologic or medical management, and evidence is insufficient to comment on effects of such interventions." To be fair, the review only included studies after 1990. There were a number of studies conducted during the decade of the 1980's demonstrating first line pharmacologic therapies were beneficial (oxytocin, PGE2, ergonovine/oxytocin combination) and these were not assessed by the review. I recommend that these be obtained and included in some fashion. A comment can be made that tempers the somewhat harsh admonition that studies are inadequate. | As noted, few studies of medical management met our review criteria; thus our ability to comment on any findings is clearly limited. We did not systematically review the older literature; however, we do note in the report's introduction and discussion sections that medical management is the standard first line. |

| Commentator & Affiliation | Section | Comment   | Response  |
|---------------------------|---------|---|---|
| TEP Reviewer #2           | General | Page 16 line 48 to page 17 line 17. In this section of the Executive Summary, there are many abbreviations for pharmacologic therapies that appear for the first time. I realize these are in the abbreviations appendix, but convention states that they should be spelled out the first time they appear in the text. This may also be true for other parts of the document. Readers can more easily understand and get through the document if they do not have to skip forward to the abbreviation appendix for each of these terms.  | We have eliminated all non-standard abbreviations.  |
| TEP Reviewer #2           | General | Page 17 line 3. The term “disseminated intravascular coagulation” is a diagnosis of exclusion and refers specifically to the situation that occurs with abruption where thromboplastic substances are leached into the maternal vascular system from the concealed clot within the uterus and prod the clotting cascade into overdrive. The situation where coagulopathy occurs after major hemorrhage is due to the loss of coagulation factors and not a “disseminated intravascular coagulation”. I believe this term is used incorrectly by most of the obstetricians and physicians in the country. I recommend one of the following terms: “coagulopathy associated with major hemorrhage”, “dilutional coagulopathy”, or simply “coagulopathy”. My preference is “dilutional coagulopathy” because it is more specific to this circumstance and is unlikely to be confused with any other cause of coagulopathy. | This is a valid point; however, we have used terminology as reported in each study and cannot make assumptions that changing the language would accurately represent the study populations. We acknowledge that some women described as having disseminated intravascular coagulation (DIC) may, in fact, have had dilutional coagulopathy associated with major hemorrhage, without DIC. |
| TEP Reviewer #2           | General | Page 17 line 41 and many other places in the manuscript. The term “initial second line procedure” may be confusing. The authors have not clearly defined that there are first line and second line therapies, nor that there are multiple “second line” options that can be used in sequence. Also, there is not any discussion of “subsequent second line therapies”. I believe the term “second line procedure” or “second line therapy” suffices. The authors should look at the document carefully to decide whether “initial” is necessary, and if so, make more clear to readers any distinction.   | We deliberately used “initial” as some women may undergo multiple procedures or surgeries considered to be second-line. We also defined success of an intervention as control of bleeding without need for further procedures or surgeries, so the use of “initial” is meaningful.  |

| Commentator & Affiliation | Section | Comment   | Response   |
|---------------------------|---------|---|--|
| TEP Reviewer #2           | General | Page 18 line 41 and page 24 line 10. "Lesion" is not the correct term here. The correct term is probably "injury" or "damage" for both bladder and ureteral injury.   | We used the terminology as reported.   |
| TEP Reviewer #2           | General | Page 21 line 51. Under "findings" in this table, the authors state: "Inconsistency in direction of effect (greater LOS and ICU admission in transfusion or whole blood groups in 2 studies; no group differences in another study)." Showing an increase in the outcome measure (greater LOS and ICU admission) in 2 studies and no difference in another study does not show any inconsistency in direction of effect. An example of inconsistency of direction of effect would be greater LOS in 2 studies and decreased LOS in another study. -More specific information should be placed here to actually show the inconsistency of direction of effect or rephrase this statement. | The finding of no significant differences in a study is a finding, thus the direction of effects differed.   |
| TEP Reviewer #2           | General | Page 22 line 31. Suggested change for clarity: "Generally SOE was insufficient given diversity of harms reported BETWEEN single studies."   | Thank you for your comment. We do not agree that the change to between or among improves clarity and have retained the original wording.   |
| TEP Reviewer #2           | General | Page 22 line 50. Spelling correction: "thromboTic".   | Corrected  |
| TEP Reviewer #2           | General | Page 23 lines 9, 16 and 26 (Table C) and page 25 lines 20, 26 and 28 (Table E). In "findings" study limitations are described on a scale from "low" to "high". I believe this is not a good scale to use, because "low" might suggest "not good" when in actuality this is desired. I suggest using a different scale, such as "minimal", "moderate" and "significant".   | The report follows AHRQ EPC methodologic standards and terminology, but we have added a table note to clarify this point.  |
| TEP Reviewer #2           | General | Page 27 line 25-38. I believe this may be the most important paragraph in the document. Society tends to want perfection in outcomes in all aspects of medicine and the reporting of improvements in medical care. This point about the rates of poor outcomes or the incidence of disease not being able to be driven below a biologically determined "floor" of occurrence should be highlighted in the conclusion.   | Thank you for your comment. Because we did not explicitly study the existence of a "floor," but noted it as a need for future research, we did not add this point to the conclusions, which focus on summing up the report's key findings. |

| Commentator & Affiliation | Section | Comment   | Response  |
|---------------------------|---------|---|---|
| TEP Reviewer #2           | General | Page 27 lines 47-48. Grammar correction. "Management was not well described in many studies, especially in for women who transferred from other hospitals."   | Corrected   |
| TEP Reviewer #2           | General | Page 28, line 54. Conclusions. Use of the word "emergent" might be confusing, because of the differing uses of the word, which can mean "in an emergency" and can also mean "emerging" or "coming to fruition". I recommend choosing a different word or phrase to convey your meaning.   | We have eliminated use of emergent.   |
| TEP Reviewer #2           | General | Page 58 line 43. I suggest changing the phrase here (and wherever this phrase appears in the rest of the text) to "uterine balloon tamponade" to distinguish between bimanual uterine compression (which might be called tamponade) and balloon devices.  | We have added balloon tamponade consistently.   |
| TEP Reviewer #2           | General | Page 127 line 15. I recommend changing the phrase "first second line intervention". "First second"? See comment number 5 above.   | We have changed this to "initial."  |
| TEP Reviewer #3           | General | The report was very with regard to reviewing quality research related to OB hemorrhage and its conclusions are similar to what others have already said that there is really no level 1 evidence and most interventions are small.  | Thank you for your comment.   |
| TEP Reviewer #3           | General | One key question not addressed is what in the absence of available clear data should be done today v. what should be done in the future.  | Thank you for your comment. This review is not intended to make practice guidelines but may be used by other groups or individuals to inform the development of guidelines. |
| TEP Reviewer #3           | General | It would also be import to further emphasize the large variation in etiologies of PPH.  | We have added some additional points to the Introduction.   |
| Peer reviewer #1          | General | The report is exceptionally well done. The key questions are well defined highly relevant clinically. The report clearly shows how underdeveloped the evidence is to guide clinicians in dealing with this very common obstetrical complication. Hopefully this report will serve to motivate more clinical research to be done in this area. | Thank you for your comment. We hope that the report will spur further research.   |

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| Commentator & Affiliation | Section | Comment  | Response   |
|---------------------------|---------|--|--|
| Peer Reviewer #2          | General | <p>An analysis of the diagnosis and treatments of postpartum hemorrhage will continue to be challenging until there is consensus on 2 fundamental questions. The first question is, what is a postpartum hemorrhage? The great difficulty in defining postpartum hemorrhage is that many studies and guidelines from National organizations use definitions primarily based on the study by Pritchard in 1962 using chromium labeled red blood cells in which he found that the average blood loss following a vaginal delivery was 500 ml and 1000 ml following a cesarean delivery.</p> <p>Therefore blood loss in excess of 500 ml for a vaginal delivery and &gt;1000 ml following a cesarean delivery are labelled as a PPH. ACOG uses the definition of &gt;500 for a vaginal delivery and &gt; 1000 for a cesarean delivery, RANZCOG uses &gt; 500 ml and severe PPH as &gt; 1000 ml, RCOG uses minor as 500-1000 ml, moderate as 1000 - 2000 ml and severe as &gt; 2000 ml, and the SGOC uses any amount threatening hemodynamic instability.</p> <p>In a normal pregnancy the plasma volume increase by approximately 50% and the red blood cell volume by 20%. If we clinically stage hemorrhagic shock by volume of blood lost, a blood loss of up to 900 ml or up to 20% of the circulating blood volume cause no change in either the maternal blood pressure or the maternal pulse. Only with the loss of up to 25% of the blood volume or approximately 1200 - 1500 ml do we observe a mild maternal tachycardia (pulse &lt; 100 beats per minute) and mild hypotension which would warrant some type of therapy if the blood loss continues.</p> <p>Moderate shock secondary to PPH occurs when 30-35% of blood volume is lost and this occurs when 1800-2100 ml of blood is lost. Maternal tachycardia is present (100-120 beats/min and maternal hypotension (systolic blood pressure of 80-100 mm Hg) at that volume of blood loss.</p> | <p>Thank you for your comment. We agree that diagnosis of PPH is complex and variable and have strengthened our discussion of those elements in the report's introduction and discussion sections.</p> |

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| Commentator & Affiliation | Section | Comment   | Response  |
|---------------------------|---------|---|---|
|                           |         | <p>In a normal pregnant patient a total blood loss of 500 or even 1000 ml is clinically insignificant. Therefore to use definitions that are clinically not significant and then compare different treatments in managing a patient with diagnosed PPH is meaningless. Only with a standard definition of PPH can we have important comparisons of outcomes.</p> <p>The use of a blood loss definition, in which, there is mild shock (20-25% blood loss volume or 1200 - 1500 ml of blood) would appear to be a threshold to define a PPH in normal women with an average blood volume of approximately 6000 ml.</p>   |   |
| Peer Reviewer #2          | General | <p>The second critical question is how the amount of the blood loss is determined. Over all it has been shown that blood loss calculation, if done meticulously, is representative of the maternal blood loss. These calculations can be done in a vaginal delivery by using the drapes that have an incorporated plastic collection bag that can collect the blood to be measured and by weighing the sponges and lap pads used at delivery both wet and dry and then calculating the blood loss by the increased weight of the pads and sponges. At the time of a cesarean delivery, blood loss can be measured by using the plastic drapes that contain pockets to collect the blood, measuring the amount of blood in the suction containers and by weighing lap pads and sponges both wet and dry and then calculating the blood loss by the increased weight of the pads and sponges. To compare studies in which the blood has been precisely measured and compare treatments with studies in which the blood loss is estimated by the health care provider, or estimated by the health care provider based on how soaked lap pads and sponges are, or to only use pre-delivery and post-delivery hematocrits to estimate blood loss seriously compromises the validity of any results comparing different methods of controlling postpartum hemorrhage.</p> | <p>Thank you for your comment. We agree that estimation of blood loss in PPH is complex and variable and have strengthened our discussion of those elements in the report's introduction and discussion sections.</p> |

| Commentator & Affiliation                         | Section | Comment   | Response   |
|---|---------|---|--|
| <b>TEP Reviewer #4</b>                            | General | The report is clear and the topic and population are clinically meaningful.   | Thank you for your comment.  |
| <b>Public Reviewer #1<br/>Suzan Ulrich</b>        | General | Determining the most effective treatment for postpartum hemorrhage (PPH) is critical to reducing maternal mortality because PPH is one of the leading causes of maternal mortality. This systematic review of the evidence attempts to determine effectiveness of treatments for postpartum PPH both non-surgical and surgical and identify harms related to these treatments.  | Thank you for your comment.  |
| <b>Public Reviewer #1<br/>Suzan Ulrich</b>        | General | Fifty-two unique studies were included in this review, and they were identified by accepted techniques. Most studies were not of good quality and there were few randomized controlled trials. PPH is a difficult topic to study because of varying definitions, the emergency nature of the event, difficulty measuring blood loss, and subjective nature of the diagnosis. The results were tempered by the fact that the majority of studies lacked strength of the evidence to support the outcomes. The studies did not directly compare treatment options or the sequencing of these interventions. The authors identified the gaps in the research and made good recommendations for future research. This carefully prepared report illustrates that currently there is not clear evidence for best practices or the appropriate intervention trajectory to obtain the best result with the least amount of harm for women experiencing PPH. Thank you for the opportunity to submit comments on behalf of the American College of Nurse-Midwives. Please feel free to contact me if there are any questions or concerns. | Thank you for your comment.  |
| <b>Public Reviewer #3<br/>Mark Turrentine, MD</b> | General | There will soon be published a national patient safety bundle on obstetrical hemorrhage (National Partnership for Maternal Safety: Consensus Bundle on Obstetric Hemorrhage). That report would benefit from the information provided in this report. Any chance this information could be forwarded to those individuals?  | Thank you for your comment. Our Technical Expert Panel included one individual who worked on the bundle, and we will work with AHRQ to ensure that the report is widely distributed. |

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| Commentator & Affiliation | Section      | Comment  | Response                     |
|---------------------------|--------------|--|------------------------------|
| Peer reviewer #3          | General      | The manuscript submitted to the AHRQ Evidence-based Practice Center Program titled "Management of Postpartum Hemorrhage" is drawn from 2,810 nonduplicative references, of which 832 went to full text review, and of which 52 unique studies were included in the review. Overall, the paper is well-written and organized. | Thank you for your comment.  |
| TEP reviewer #5           | General      | The review is thorough, excellent and well done! Congratulations.  | Thank you for your comments. |
| TEP reviewer #5           | General      | The review will be very useful for highlighting the many research limitations related to the management of a common cause of maternal mortality and morbidity in the United States.  | Thank you for your comments. |
| TEP reviewer #5           | General      | I look forward to having this report publicly released and hope that it will form the foundation for additional research into the management of postpartum hemorrhage.   | Thank you for your comments. |
| TEP Reviewer #2           | General      | Page 51 line 26. The phrase "third line treatment" appears for the first time here. I would recommend the authors more clearly define what is meant by "first line", "second line" and "third line" treatments.  | Corrected                    |
| TEP Reviewer #1           | Introduction | Scope and key questions are well presented tables and figure enhance clarity   | Thank you for your comment.  |
| Key Informant #1          | Introduction | Clear and concise introduction   | Thank you for your comment.  |
| TEP Reviewer #2           | Introduction | Appropriate and concise  | Thank you for your comment.  |
| TEP Reviewer #3           | Introduction | No specific concerns   | Thank you for your comment.  |

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| Commentator & Affiliation | Section      | Comment   | Response   |
|---------------------------|--------------|---|--|
| Peer reviewer #1          | Introduction | ES3: Hysterectomy eliminates the primary source of obstetrical bleeding. I am not certain that it makes sense to talk about success rates with respect to hysterectomy in controlling PPH. Considerations should also be given to whether it makes sense to compare hysterectomy, which provides definitive therapy, with other approaches to treating PPH like embolization and uterine compression sutures. | We reported rates of success in studies that indicated that no further interventions were needed, but we agree that the rates may be difficult to interpret for a “final” intervention such as hysterectomy. We have removed the table of success rates.   |
| Peer Reviewer #2          | Introduction | Satisfactory  | Thank you for your comment.  |
| TEP Reviewer #4           | Introduction | Well written.   | Thank you for your comment.  |
| Peer reviewer #3          | Introduction | Page 10 Line 42 It appears ACOG is spelled out in full, but not abbreviated at its first mention.   | To distinguish between the American College of and American Congress of Obstetrics and Gynecology, we spelled those out rather than use an acronym.  |
| Peer reviewer #3          | Introduction | Page 16 Line 51 Some terms are first mentioned as abbreviations, but not spelled out (e.g. TXA, rTM).   | We have eliminated non-standard abbreviations.   |
| Peer reviewer #3          | Introduction | Page 17 Line 16 It would be more appropriate to discuss ecbolic agents (i.e. oxytocin, prostaglandins, etc) which are intended to be treatments for the primary etiology of PPH (uterine atony), separately from procoagulant drugs (i.e. tranexamic acid, thrombomodulin, rFVIIA, etc) which are intended for secondary coagulation defects stemming from PPH, of whatever cause.                            | Findings related to these drugs are discussed separately in the Main Report; however, as few studies addressing each of these agents, the strength of the evidence for each agent was insufficient, and we provided an overall summary statement in the Executive Summary to be cognizant of space limitations. We have clarified that the SOE finding is for each individual agent. |

| Commentator & Affiliation | Section      | Comment  | Response   |
|---------------------------|--------------|--|--|
| Peer reviewer #3          | Introduction | Page 17 Line 20 The Authors appropriately use the term “management” with regard to transfusion for PPH, and later in the manuscript discuss the issue of transfusion as a complication. This Reviewer believes it important that transfusion not be considered a treatment for PPH (transfusion does not correct the underlying problem of atony, lacerations, retained placenta, etc), but rather a supportive measure (such as crystalloid infusion and oxygen supplementation). | We have emphasized that transfusion is used for supportive management of PPH in our summary of results. Some studies did report on need for transfusion as an outcome. |
| Peer reviewer #3          | Introduction | Page 34 Line 44 It would be reasonable to include platelet concentrates in the transfusion comments.   | We have added this to Table 1.   |
| Peer reviewer #3          | Introduction | Page 35 Line 44 Placenta accreta/increta/percreta, given its increasing incidence and high morbidity, should be mentioned here.  | We have revised the KQ wording.  |
| Peer reviewer #3          | Introduction | Page 36 Line 18 Currently there are at least 3 commercially available FDA-cleared balloon tamponade devices (Bakri, BT Cath, and Belfort-Dildy Obstetrical Tamponade System), whereas the other devices mentioned here (Foley, S-B tube, Rusch balloon) are not FDA-cleared for the indication of PPH. Consideration should be given to discuss the 2 categories separately.   | We grouped these devices in the table referenced here but describe any studies addressing them separately in the text.   |
| Peer reviewer #3          | Introduction | The Introduction is of appropriate content.  | Thank you for your comments.   |
| TEP Reviewer #1           | Methods      | Quality assessment of individual studies was quite rigorous strength of evidence grades and definitions were clearly presented   | Thank you for your comment.  |
| TEP Reviewer #1           | Methods      | Was abnormal placentation encompassed by retained placenta?  | We have revised the KQ to include abnormal placentation.   |
| Key Informant #1          | Methods      | Methods are clearly defined and logical for this systematic review. Inclusion and exclusion criteria are well defined and make sense.  | Thank you for your comment.  |
| TEP Reviewer #2           | Methods      | See comment numbers 5, 6, 7, 11, 14, 15, 16, and 17 above.   | Thank you for your comment.  |

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| Commentator & Affiliation | Section | Comment  | Response   |
|---------------------------|---------|--|--|
| <b>TEP Reviewer #3</b>    | Methods | This was clearly defined   | Thank you for your comment.  |
| <b>Peer reviewer #1</b>   | Methods | Are the inclusion and exclusion criteria justifiable?<br>Yes   | Thank you for your comment.  |
| <b>Peer reviewer #1</b>   | Methods | Are the search strategies explicitly stated and logical?<br>Yes  | Thank you for your comment.  |
| <b>Peer reviewer #1</b>   | Methods | Are the definitions or diagnostic criteria for the outcome measures appropriate?<br>Yes. Across many studies the outcomes reported are confounded by the underlying severity of the PPH, but the authors are careful to point this out.                            | Thank you for your comment.  |
| <b>Peer Reviewer #2</b>   | Methods | Yes  | Thank you for your comment.  |
| <b>TEP Reviewer #4</b>    | Methods | Inclusion and exclusion criteria and outcome measures seem appropriate to me, but I was a key informant and technical expert panel member, so we went over these in advance of the report. Outside reviewers might be in better position to address this question. | Thank you for your comment. External reviewers not involved in the expert panel have also reviewed the report (listed as peer reviewer #X in this document). |
| <b>TEP Reviewer #4</b>    | Methods | Other methods appear appropriately conducted and are clearly described.  | Thank you for your comment.  |
| <b>Peer reviewer #3</b>   | Methods | The inclusion/exclusion criteria are reasonable. Outcome measures are appropriate. Prophylactic versus therapeutic interventions for PPH should be differentiated.   | Thank you for your comments. As noted, where this distinction was made in studies, we reported it in our analysis.   |
| <b>TEP Reviewer #1</b>    | Results | Figure 2 is masterful in this section.   | Thank you for your comment.  |
| <b>TEP Reviewer #1</b>    | Results | The investigators construct a detailed strategy that convinces the reader that meta-analysis, the logical choice for a statistical approach all of these questions and sub-questions would not be appropriate  | Thank you for your comment.  |

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| Commentator & Affiliation | Section | Comment  | Response   |
|---------------------------|---------|--|--|
| TEP Reviewer #1           | Results | Hysterectomy success rates are difficult to interpret due to the underlying disease process causing hemorrhage and the fact that they are implemented as a salvage procedure when all else fails and every attempt was made to avoid this intervention | We reported rates of success in studies that indicated that no further interventions were needed, but we agree that the rates may be difficult to interpret for a “final” intervention such as hysterectomy. We have removed the table of success rates and made revisions to the text to provide clarification. |
| TEP Reviewer #1           | Results | Harms of interventions are perhaps the most challenging to quantify and analyze since the disease process such as abnormal placentation leading to hysterectomy drives the overall severity of hemorrhage and complications from interventions         | Thank you for your comment. We agree that determining the underlying cause of a harm (the PPH or the intervention) is challenging and thus reported only those harms reported as due to the intervention in the studies meeting our criteria.  |
| Key Informant #1          | Results | Results relate directly to the key questions (except KQ2), no studies supporting this question.  | Thank you for your comment.  |
| Key Informant #1          | Results | Details are appropriate and clear as relates to each KQ.   | Thank you for your comment.  |
| Key Informant #1          | Results | Tables are descriptive and clear   | Thank you for your comment.  |
| TEP Reviewer #2           | Results | See comment numbers 2, 3 and 11 above.   | Thank you for your comment.  |
| TEP Reviewer #3           | Results | With regard to toolkits the CMQCC toolkit is not reference unless I missed it.   | We have referenced the toolkit in the Introduction.  |
| TEP Reviewer #3           | Results | Also if the goal of the project was provide guidance on how to manage PPH based on the data presented I did not walk away with that message.   | The review is not intended to provide guidelines for care, though other organizations or clinicians may use it to develop guidance.  |
| Peer reviewer #1          | Results | Is the amount of detail presented in the results section appropriate?<br>Yes   | Thank you for your comment.  |

| Commentator & Affiliation | Section | Comment   | Response   |
|---------------------------|---------|---|--|
| Peer reviewer #1          | Results | Are the characteristics of the studies clearly described?<br>Yes  | Thank you for your comment.  |
| Peer reviewer #1          | Results | Are the key messages explicit and applicable?<br>Yes  | Thank you for your comment.  |
| Peer reviewer #1          | Results | Are figures, tables and appendices adequate and descriptive?<br>Yes   | Thank you for your comment.  |
| Peer reviewer #1          | Results | Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded?<br>There is a new study examining systems-level interventions that is in press at Am J of Obst Gynecol (Shields LE, Am J Obstet Gynecol. 2014 Jul 12) that likely came out after the literature search. This is a seemingly well done pre- post- study that does show some effect for systems-level interventions. | We added this study while the report was undergoing peer review.   |
| Peer reviewer #1          | Results | In considering systems-level interventions, it may be worth discussing the evidence for the importance of the setting for delivery on the risk of morbidity for cases of peripartum hysterectomy/accreta (e.g., Wright et al. Obstet Gynecol. 2010;115:1194–1200; Eller et al. Obstet Gynecol. 2011.117(2 Pt 1):331-7).   | We agree that this is an important point and have noted the potential effects of setting on morbidity in the Introduction. |
| Peer reviewer #1          | Results | Page ES-9, line 12. Consider providing more detail regarding what constitutes "medical" and "surgical" management in this example.  | We have added some examples.   |
| Peer reviewer #1          | Results | Page ES-10, line 51. I would add carboprost to this list of most commonly used uterotonics (see ref 31)   | We have added carboprost to this list in the Executive Summary.  |
| Peer reviewer #1          | Results | Page ES-13. Consider discussing methergine and the risk of MI in the discussion of harms given the attention that was brought to this issue with the relatively recent Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) in 2012 and the subsequent change to the label   | Harms reported in the review were limited to those reported in the studies included.                                       |
| Peer reviewer #1          | Results | ES-18, line 15. Other relevant effect modifiers might include following induction and/or prolonged oxytocin infusion  | Thank you for pointing these out. We have added them to the future research section.                                       |

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Published Online: April 28, 2015

| Commentator & Affiliation | Section | Comment  | Response   |
|---------------------------|---------|--|--|
| Peer reviewer #1          | Results | Page ES-18, line 26-39. I think the ideas in this section are rich, but need to be fleshed out a bit so they are clear to the reader. How can risk adjustment methods be used to define the "floor"? are there cohorts in the literature that can be subject to this kind of metaanalysis?   | We have added addition description of risk adjustment as a concept. Meta-analysis to determine the contribution of a specific component does not contribute information if the intervention components are all the same. So unfortunately, this means that some of the studies that used identical interventions in different population can be used to estimate the effects of that system level intervention as delivered but cannot help tease apart the active ingredients. It is possible that given the continuity of the French obstetrics research data and some variation in the interventions that the RCT and observational studies could be combined, and risk adjustment approaches used, but the sheer scale of the trial and its null results for primary outcomes means that the overall aggravate results would likely be null. For space reasons, we have not dedicated any discussion to the nuances of why current studies are less than ideal for meta-regression or meta-analysis. { |
| Peer reviewer #1          | Results | Page 3, Hysterectomy--I don't think it is quite right to say that hysterectomy may be ineffective when percreta is present. Hysterectomy is necessary in these cases, but other interventions will be required to stop bleeding.   | We have deleted the sentence.  |
| Peer reviewer #1          | Results | Page 46/50. As noted above, I am not sure it is meaningful to talk about the "success" of hysterectomy. While additional procedures may well be required, hysterectomy is the only approach that will definitively remove the major source of bleeding with PPH. Particularly with percreta, additional procedures may be required, but hysterectomy will be an essential part of the management of these cases. | We reported rates of success in studies that indicated that no further interventions were needed, but we agree that the rates may be difficult to interpret for a "final" intervention such as hysterectomy. We have removed the table of success rates.   |

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|---------------------------|---------|--|--|
| Peer reviewer #1          | Results | Page 66. In the cluster randomized trial, could it be that passive diffusion protocols in the control arm of the study might bias the results to the null?   | This point can be a concern in some cluster randomized designs. In this instance, because the level of randomization for this trial was the hospital, and the hospitals spanned maternity regions in France it seems unlikely that the control hospitals put into place key components of the intervention (education events were not held, materials were not available, etc.). Table 3 of the RCT also shows that the control sites did not increase use of selected key protocol elements like calling for help of senior staff, administration of sulprostone, or testing hemoglobin/hct levels, suggesting they were not implementing the protocol. Thus, we did not have concerns about contamination of the control group for this trial. |
| Peer reviewer #1          | Results | Does this intervention [Page 66. cluster randomized trial] really test the effectiveness of systems-level approaches or just the reinforcement of these approaches with academic detailing, protocol reminders, and peer review?   | This study tests a complex package of intervention components, and these sorts of components (academic detailing, protocol tracking, etc) are typical of systems-level safety interventions, which are generally evaluated as a whole program. Items that might be considered individual components are reviewed in the area of the report that takes on RCTs of specific tools/interventions.   |
| Peer reviewer #1          | Results | Page 94. It is notable that the confidence intervals for the estimates associated with most of these studies are very wide. While the lack of power is alluded to in the paragraph, this issue could be made more prominent as it really informs the interpretation of the results regarding the efficacy of misoprostol | The data noted here are not confidence intervals but the range of harms reported.  |

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Published Online: April 28, 2015

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|---------------------------|------------------------|--|--|
| Peer reviewer #1          | Results                | Page 95, line 48. Does SES have an important bearing on the generalizability of this result? Why is this expected to be an important effect modifier?  | We have deleted the sentence.  |
| Peer Reviewer #2          | Results                | Yes  | Thank you for your comment.  |
| TEP Reviewer #4           | Results                | Studies are clearly described, tables are very helpful.  | Thank you for your comment.  |
| Peer reviewer #3          | Results                | Page 22 Line 14 Even though the number of cases reported is small, uterine artery ligation should be analyzed separately from the hypogastric artery ligation, as the latter is technically more difficult, associated with greater potential morbidity, rarely taught anymore, and probably less effective than the former. | Because studies did not present results separately for each type of ligation, we describe all results together; however, we have clarified in the text what types of ligation were used.   |
| Peer reviewer #3          | Results                | Page 24 Line 8 The term “secondary hysterectomy disunion” is one which many Readers may be unfamiliar.   | We agree, but this is how the harm was reported in the study. We have noted that the term was not clearly defined.   |
| Peer reviewer #3          | Results                | Page 24-46 Also time limitations to proceed to the next intervention will be critical in study design, because in many of these retrospective studies, timing was highly variable.   | We agree and have added this to the Research Gaps section.   |
| Peer reviewer #3          | Results                | The detail appears to be appropriate. I cannot think of any critical exclusions.   | Thank you for your comments.   |
| TEP Reviewer #1           | Discussion/ Conclusion | Syntax error line 21 p 107 or in place of “of”   | Corrected  |
| TEP Reviewer #1           | Discussion/ Conclusion | The conclusions regarding the overall low quality and absence of dated is well presented in great detail   | Thank you for your comment.  |
| TEP Reviewer #1           | Discussion/ Conclusion | The last recommendation is quite provocative regarding the realization of a “floor” for hemorrhage I have concerns about whether meta-analysis will ever be possible even when this concept is utilized  | Meta-analysis of this literature would seem to be forestalled predominantly by the heterogeneity of the components of the models and the differences in the underlying structures of care. |

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 Published Online: April 28, 2015

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|---------------------------|------------------------|---|---|
|                           |                        |   | <p>Heterogeneity in the components means that an analysis attempting to isolate the contribution of the component would be ideal. In some instances this reduces the number of studies contributing data to 2 or 3. Even when 4 or more studies deploy a similarly classified tactic/component, for instance checklists or tools for tracking care, the content of the tool, the time it is intended to be deployed (e.g. on admission and throughout care or in response to increased bleeding), the individuals using them, and the goal of the checklist (accelerate response, document interventions, measure blood loss) are varied and may be poorly suited to estimating aggregate effects. Meta-regression of such large datasets taking into account variations in underlying risk of incident hemorrhage such as induction of labor, length of labor, placental abnormalities, multiparity, etc., could more accurately define the contributions of the interventions. We concur that this is not currently possible but could be in the future through alignment of protocols for subsequent research.</p> |
| TEP Reviewer #1           | Discussion/ Conclusion | Methods for dealing with confounding by indication should be explored in more detail How would simulation and logistic regression aid study design? | We have added discussion of meta-regression as a risk adjustment approach. Simulations using extant data would serve a similar purpose for estimating the degree of influence of a specific population prevalence characteristic on the outcomes (for instance simulating the influence of induction of labor on the effects of intervention among a  |

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|---------------------------|---------------------------|---|---|
|                           |                           |   | subset of participants such as only those with vaginal births, excluding cesarean which in some studies are currently grouped together. We have added this point as a candidate for future needs for control of confounding:  |
| <b>Key Informant #1</b>   | Discussion/<br>Conclusion | Implications are clear, well defined studies of good quality are necessary to improve management and outcomes for PPH.  | Thank you for your comment.   |
| <b>Key Informant #1</b>   | Discussion/<br>Conclusion | Limitations are well described.   | Thank you for your comment.   |
| <b>TEP Reviewer #2</b>    | Discussion/<br>Conclusion | See comment numbers 3, 12 and 14 above.   | Thank you for your comment.   |
| <b>TEP Reviewer #3</b>    | Discussion/<br>Conclusion | If one was to take the findings literally there would be no intervention for PPH due to the SOE. I would strongly encourage the authors to consider how they might include analysis of the reports using systematic approaches to PPH (NY, CMQCC, and Dignity Health)                               | We did include systems-level studies in the review (KQ5). We note that the strength of the evidence should not be used as a proxy for the effectiveness of an intervention but rather our confidence in the likelihood that future studies may change the findings of studies included in the review. |
| <b>TEP Reviewer #3</b>    | Discussion/<br>Conclusion | The results of approach used by Dignity Health was good (not included due to publication after citation collection). At the moment even getting hospitals to implement consensus opinion programs related to PPH is difficult but as noted above appear to make significant difference in outcomes. | We added this paper during the peer review process.   |
| <b>TEP Reviewer #3</b>    | Discussion/<br>Conclusion | Future goals should be to look critically at new medications that can be added in RTCs. No one is going to stop using methergine, hemabat, cyttoec based on this report.  | We have added a point to the future research section.   |
| <b>Peer reviewer #1</b>   | Discussion/<br>Conclusion | Are the implications of the major findings clearly stated?<br>Yes   | Thank you for your comment.   |

| Commentator & Affiliation           | Section                | Comment   | Response  |
|-------------------------------------|------------------------|---|---|
| Peer reviewer #1                    | Discussion/Conclusion  | Are the limitations of the review/studies described adequately?<br>Yes  | Thank you for your comment.   |
| Peer reviewer #1                    | Discussion/Conclusion  | In the discussion, did the investigators omit any important literature?<br>No   | Thank you for your comment.   |
| Peer reviewer #1                    | Discussion/Conclusion  | Is the future research section clear and easily translated into new research?<br>Yes, in general. See above comment regarding the final section of the directions for future research   | Thank you for your comment. We have expanded our discussion of the future research points noted.  |
| Peer Reviewer #2                    | Discussion/Conclusion  | In the discussion need to further discuss the fundamental questions noted above that currently limits investigations of postpartum hemorrhage. A universally accepted definition of postpartum hemorrhage and a universally accepted method to measure the blood loss | Thank you for your comment. We agree that estimation of blood loss in PPH is complex and variable and have strengthened our discussion of those elements in the report's introduction and discussion sections.  |
| TEP Reviewer #4                     | Discussion/Conclusion  | Implications and limitations of the literature are clearly described. Recommendations for future research are clearly delineated and thorough.  | Thank you for your comment.   |
| Public Reviewer #2<br>Lauren Plante | Discussion/Conclusion  | Systems-level interventions to reduce PPH should include systems level interventions to reduce the cesarean rate.   | Thank you for your comment. We note that this review was focused on treatments for PPH and that AHRQ has published a review of interventions to reduce cesarean births in low risk pregnancies. See <a href="http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&amp;productid=1291">http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&amp;productid=1291</a> |
| Peer reviewer #3                    | Discussion/Conclusions | Page 85-20 The subsequent adverse effect of spontaneous abortion in the next pregnancy is no higher than general background rate.   | We noted this in the strength of the evidence table and discussion of harms.  |
| Peer reviewer #3                    | Discussion/Conclusions | Page 86 Line 51 There appears to be an extra zero (0) in one of the denominators.   | Corrected, thank you.   |
| Peer reviewer #3                    | Discussion/Conclusions | Page 129-44 It is important to differentiate prophylactic versus therapeutic interventions for PPH throughout this manuscript.  | Where studies differentiated this, we reported it.  |

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Published Online: April 28, 2015

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|---------------------------|----------------------------|---|--|
| <b>Peer reviewer #3</b>   | Discussion/<br>Conclusions | At the end of this exhaustive review, the Authors conclude that there is limited high-quality evidence regarding best practices for PPH, one of the most common complications of pregnancy, and a leading killer of otherwise healthy young women in the United States. In this Reviewer's opinion, well-organized and well-funded multi-institutional research networks (e.g. The MFM Units Network) would be the best hope for sorting out the multitude of questions regarding timing and sequence of interventions for PPH, while controlling other aspects of the "trajectory of care". Thank you very much for requesting my review of this interesting manuscript  | Thank you for your comments.                                   |
| <b>Peer reviewer #3</b>   | Discussion/<br>Conclusion  | Implications of major findings could be better delineated. Most cases of PPH mortality are preventable; what are the implications if systems level interventions could reduce avoided mortality and severe morbidity?   | This is beyond the scope of the current review.                |
| <b>TEP reviewer #5</b>    | Discussion                 | I was pleased to see that on page 27 you highlight one of the research gaps to be: "Using and clearly reporting objective methods to diagnose PPH, including accurate measurement of blood loss. Visual estimation of blood loss is too imprecise to be used in research."  | Thank you for your comments.                                   |
| <b>TEP reviewer #5</b>    | Conclusions                | I would recommend that the lack of consistently and objectively measuring blood loss is major limitation in how the studies are designed be further highlighted in the conclusion since in order to study PPH management it is necessary to have clear definitions of PPH based on objective methods of measuring blood loss. I suggest that the final sentence be re-worded to further accentuate this important point. For example the sentence could say: Further research is needed to determine the relationship of a type of interventions for PPH management, especially pharmacologic interventions which as first-line therapies are the most frequently used, compared to actual amounts of blood loss. | We have expanded the Research Gaps section to note this point. |