Evidence-based Practice Center Systematic Review Protocol
Project Title: Management of Postpartum Hemorrhage

I. Background and Objectives for the Systematic Review

Definition and Prevalence

Postpartum hemorrhage (PPH) is commonly defined as blood loss exceeding 500 mL following vaginal birth and 1000 mL following cesarean.[1] Definitions vary, however, and are often based on inaccurate estimates of blood loss.[1-4] Moreover, average blood loss at birth frequently exceeds 500 or 1000 mL.[4] Proposed alternate metrics for defining and diagnosing PPH include change in hematocrit, need for transfusion, rapidity of blood loss, and changes in vital signs, all of which are complicated by the emergent nature of the condition.[1] PPH is often classified as primary/immediate/early, occurring within 24 hours of birth, or secondary/delayed/late, occurring more than 24 hours post-birth to up to 12 weeks postpartum. In addition, PPH may be described as third or fourth stage depending on whether it occurs before or after delivery of the placenta respectively.

The overall prevalence of PPH worldwide is estimated to be 6 to 11 percent.[5, 6] Rates vary by data source and country as well as assessment method with a prevalence of 10.6 percent when measured by objective appraisal of blood loss and 7.2 percent when assessed with subjective techniques.[5] A systematic review estimated prevalence of PPH with 500 mL of blood loss or more at 10.5 percent in Africa, 8.9 percent in Latin America and the Caribbean, 6.3 percent in North America and Europe, and 2.6 percent in Asia.[5] Estimates in another systematic review were higher, with similarly wide regional variation: 26 percent in Africa, 13 percent in North America and Europe, and 8 percent in Latin America and Asia.[6] The prevalence of PPH with 1000 mL blood loss or more was considerably lower in both reviews with overall estimates of 1.9 to 2.8 percent.[5, 6] Despite lower estimates for PPH in developed countries compared with developing nations, several studies have noted an increase in PPH in high-resource regions.[7-13] In the United States, the prevalence of PPH rose from 2.3 percent in 1994 to 2.9 percent in 2006, a 26 percent increase.[14] Factors underlying the increase remain unknown; however, studies investigating changes in maternal age, obesity, mode of birth, multiple birth, duration and characteristics of labor, and placental abnormalities among other factors found that these putative observed risk factors did not account for rising PPH rates.[7, 8, 11-14]

Adverse Outcomes Associated with Postpartum Hemorrhage

PPH is one of the leading causes of maternal mortality and morbidity worldwide and accounts for nearly one-quarter of all maternal deaths.[15] Multiple studies have suggested that many deaths associated with PPH could be prevented with prompt recognition and more timely and adequate treatment.[16-18] Morbidity from PPH can be severe with sequelae including organ failure, shock, edema, compartment syndrome, transfusion complications, thrombosis, acute respiratory distress syndrome, sepsis, anemia, intensive care, and prolonged hospitalization.[19-21]

The most common etiology of PPH is uterine atony (impaired uterine contraction after birth), which occurs in about 80 percent of cases. Atony may be related to

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overdistention of the uterus, infection, placental abnormalities, or bladder distention.[22] Though the majority of women who develop PPH have no identifiable risk factors, clinical factors associated with uterine atony, such as multiple gestation, polyhydramnios, high parity, and prolonged labor, may lead to a higher index of suspicion.[19, 20, 22, 23] Other causes of PPH include retained placenta or clots, lacerations, uterine rupture or inversion, and inherited or acquired coagulation abnormalities.[22, 23]

Interventions

Organizations and associations including the World Health Organization (WHO), International Confederation of Midwives (ICM), International Federation of Gynecologists and Obstetricians (FIGO), American College of Obstetricians and Gynecologists (ACOG), and Royal College of Obstetricians and Gynaecologists (RCOG) have released guidelines for PPH prevention and management.[15, 20, 22-25] Initial management includes identifying PPH, determining the cause, and implementing appropriate interventions based on the etiology. Interventions to treat PPH generally proceed from less to more invasive and include compression techniques, medications, procedures, and surgeries. PPH management may also involve adjunctive therapies, such as blood and fluid replacement and/or an anti-shock garment,[26, 27] to treat the blood loss and other sequelae that result from PPH. In cases of severe blood loss from PPH, the hemostatic recombinant factor VIIa (NovoSeven® and AryoSeven™) and the antifibrinolytic tranexamic acid (Cyklokapron® or Lysteda®) have been used.[28]

External uterine massage and bimanual compression are generally used as first-line treatments. These compression techniques encourage uterine contractions that counteract atony and assist with expulsion of retained placenta or clots. Aortic compression is another compression technique that has been used for severe PPH. [29, 30]

The immediate postpartum period is a unique physiologic state with relative intravascular volume expansion with a reduction in cardiovascular demand compared to pregnancy. The physiologic anemia of pregnancy may be exacerbated by acute blood loss anemia from postpartum hemorrhage. These physiologic realities may allow women with low hematocrits to be asymptomatic. Interventions for acute blood loss anemia include red blood cell transfusion and iron supplementation. Erythropoietin stimulating agents (Aranesp®, Epogen®, Procrit®) have also been used for anemia following stabilization of PPH, but they are not approved by the FDA for this use.[20]

The medications most commonly used in PPH management are uterotonic agents, which cause the uterus to contract. These medications include oxytocin (Pitocin®), prostaglandin E1/misoprostol (Cytotec®), methylergonovine (Methergine®,), prostaglandin 15-methyl $F_{2\alpha}$/carboprost tromethamine (Hemabate®), and prostaglandin E2/dinoprostone (Cervidil® or Prepidil®).[15, 20, 22, 23, 31] All of these medications are available in the United States. Only oxytocin, methylergonovine, and carboprost tromethamine are approved by the FDA specifically for PPH management; use of these other medications is off label.

Procedures used in PPH management include manual removal of the placenta, manual removal of clots, uterine tamponade, and uterine artery embolization.[15, 20, 22, 23] Laceration repair is indicated when PPH is a result of genital tract trauma. Surgical options in the event of failure of other measures to control bleeding include curettage, uterine artery ligation, uterine hemostatic compression suturing, and hysterectomy.[15, 20, 22, 23] Procedures

and surgeries can increase the risk of infection and other complications, and they may eliminate or adversely affect future fertility and pregnancy. After PPH has been controlled, followup management varies and may include laboratory testing (e.g., hemoglobin and hematocrit), iron replacement therapy, and other interventions to assess and treat sequelae of PPH, including harms of treatment for PPH. Harms may include fever, vomiting, vascular perforation, uterine ischemia, thrombosis, fertility loss, and infection.

At a systems level, PPH has been the focus of perinatal care safety initiatives that attempt to improve patient outcomes by incorporating a variety of strategies, such as practice guidelines or protocols, simulation drills, and teamwork training.[32-36] These systems-level interventions may influence management of PPH.

A variety of outcomes related to PPH management are reported.[37-42] Blood loss itself is measured, although with challenges as previously noted. Transfusion and anemia are markers for the amount of blood loss. The outcomes of ICU admission and extended hospitalization are used as indicators of maternal morbidity. Severe hemorrhage can lead to hysterectomy and death.

PPH can occur in any birth setting: hospital, birth center, or home. Limited interventions for PPH are available in the out-of-hospital settings; thus this condition is an indication for transport for inpatient care. In considering setting, it is important to note that PPH management varies significantly according to available resources; therefore, many studies conducted in low-resource countries have limited to no applicability for higher-resource countries such as the United States.

Rationale for Review and Objectives

Clinicians face a number of challenges in managing PPH. The lack of a clear definition and consistent terminology can delay timely diagnosis and appropriate intervention. Treatment varies depending on the etiology, and clinicians need to know the optimal assessment methods to determine the cause. When medications are warranted, the first-line medication(s) and the order in which multiple medications should be used are unclear. Better understanding of when to proceed to procedures and surgeries as well as appropriate selection from these management options is also needed. As the nominator of this review topic notes, the goal and clinical dilemma of PPH management is to balance minimally invasive conservative treatment that preserves fertility with the need to control bleeding and achieve hemostasis.

There are a number of relevant studies available for this review as well as some previous systematic reviews. The most recent Cochrane reviews on management of primary and secondary PPH were last updated in 2007 and 2008 respectively.[37, 38] More recent systematic reviews related to PPH management are focused on specific aspects including uterine balloon tamponade in resource-poor settings,[39] emergency hysterectomy for PPH,[40] anti-fibrinolytic agents,[41] and pregnancy outcomes after surgical treatment.[42] The current review will provide a comprehensive assessment of the literature and will include eligible studies of all interventions—including systems-level approaches—for managing PPH.

II. The Key Questions (KQs)

We established our initial key questions based on our preliminary review of the literature, information from the review nominator, and information in the topic nomination. Public comments to the key questions emphasized the lack of universally accepted definitions for PPH; issues with understanding risk factors; difficulties in estimating blood loss and in accounting for the severity of hemorrhage across patients; need for better understanding of harms; and challenges in assessing systems-level interventions. Few comments necessitated changes to the key questions; however, we added subinvolution as a potential cause of PPH in KQ1d and explicitly added uterine preservation as an outcome of questions dealing with the effectiveness of interventions. We also note that we will consider future pregnancy complications in our assessment of harms.

Our key questions (KQs) are as follows:

KQ1. What is the evidence for the comparative effectiveness of interventions for management of postpartum hemorrhage?

a. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to atony?
b. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to retained placenta?
c. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to genital tract trauma?
d. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to uncommon causes (e.g., coagulopathies, uterine inversion, subinvolution)?

KQ2. What is the evidence for choosing one intervention over another and when to proceed to subsequent interventions for management of postpartum hemorrhage?

KQ3. What are the comparative harms, including adverse events, associated with interventions for management of postpartum hemorrhage?

KQ4. What is the comparative effectiveness of interventions to treat acute blood loss anemia after stabilization of postpartum hemorrhage?

KQ5. What systems-level interventions are effective in improving management of postpartum hemorrhage?

Table 1 outlines **P**opulation, **I**ntervention, **C**omparator, **O**utcomes, **T**iming, and **S**etting (PICOTS) elements for each KQ.

Table 1. PICOTS

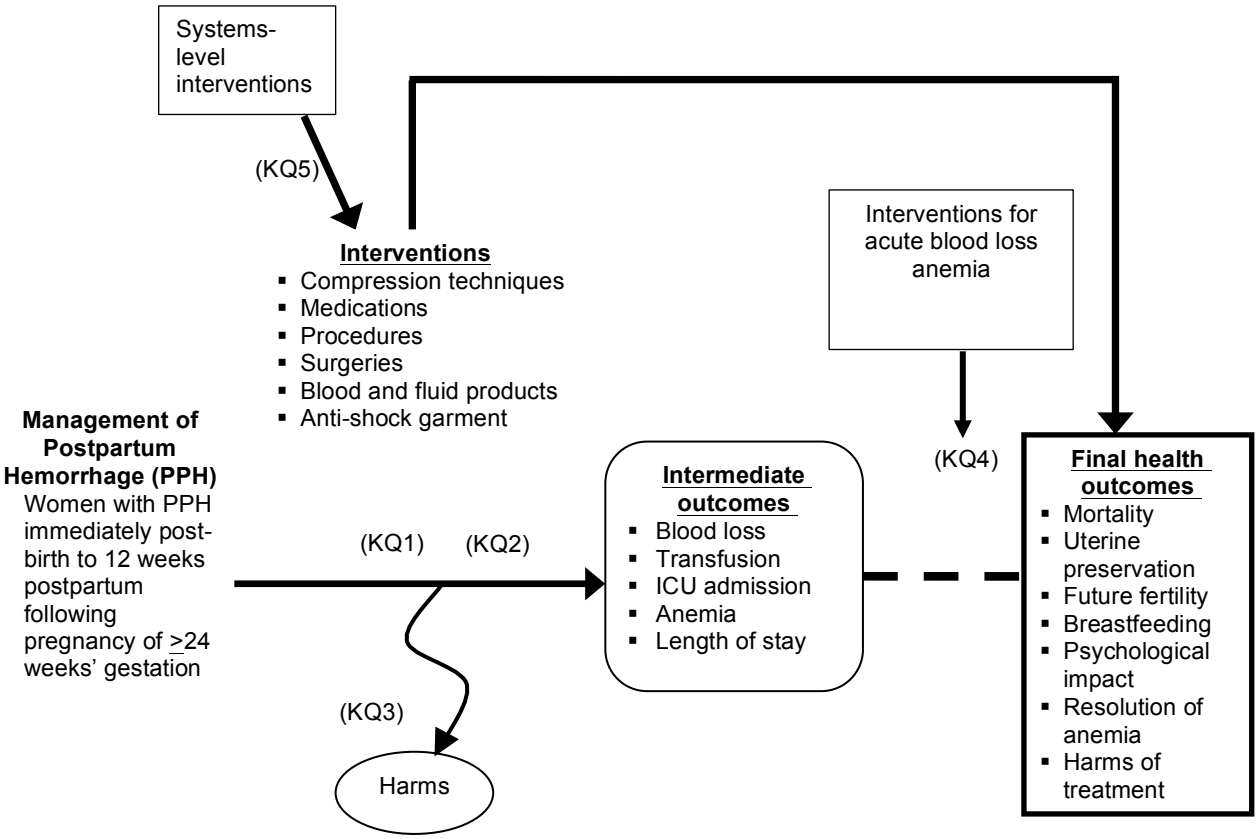
PICOTS	Criteria
Population	• KQ1-3: Women with postpartum hemorrhage (PPH) immediately post-birth to 12 weeks postpartum following pregnancy >24 weeks' gestation • KQ4: Women with stabilized PPH and acute blood loss anemia • KQ 1-5: All modes of birth
Intervention(s)	KQ1-3, 5 • Compression techniques (external uterine massage, bimanual compression, aortic compression) • Medications (oxytocin [Pitocin], prostaglandin E1 [Misoprostol, Cytotec], methylergonovine [Methergine], prostaglandin 15-methyl $F_{2\alpha}$ [Hemabate], prostaglandin E2 [Dinoprostone], recombinant factor VIIa [NovoSeven], and tranexamic acid [Cyklokapron]) • Devices (Bakri postpartum balloon, Foley catheter, Sengstaken-Blakemore tube, Rusch balloon) • Procedures (manual removal of placenta, manual evacuation of clot, uterine tamponade, uterine artery embolization, laceration repair) • Surgeries (curettage, uterine artery ligation, uterine hemostatic compression suturing, hysterectomy) • Blood and fluid products • Anti-shock garment • Systems-level interventions (e.g., implementation of protocols, training) KQ4 • Interventions for acute blood loss anemia (e.g., iron replacement, erythropoietin)
Comparator	• Different intervention (any intervention compared with any other intervention) • Placebo
Outcomes	Intermediate outcomes • Blood loss • Transfusion • ICU admission • Anemia • Length of stay Final outcomes • Mortality • Uterine preservation • Future fertility • Breastfeeding • Psychological impact • Harms
Timing	• Immediately post-birth to 12 weeks postpartum • Primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum)
Setting	• All birth settings (hospital, birth center, home)

Abbreviations: PICOTS=Population, Intervention, Comparator, Outcomes, Timing, Setting; ICU=Intensive Care Unit

III. Analytic Framework

The analytic framework illustrates the population, interventions, and outcomes that will guide the literature search and synthesis (Figure 1). The framework for Management of Postpartum Hemorrhage (PPH) includes women with PPH immediately post-birth to 12 weeks postpartum following pregnancy of >24 weeks' gestation. The figure depicts the key questions within the context of the PICOTS described in the document. In general, the figure illustrates how interventions such as compression techniques, medications, procedures, surgeries, blood and fluid products, anti-shock garments or systems-level interventions may result in intermediate outcomes such as blood loss, transfusion, ICU admission, anemia, or length of stay and/or in final health outcomes such as mortality, uterine preservation, future fertility, breastfeeding, or psychological impact. Also, adverse events may occur at any point after the intervention is received.

Figure 1. Analytic Framework



Abbreviations: KQ=key question; ICU=Intensive Care Unit

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The inclusion and exclusion criteria for the review are derived from our understanding of the literature and refinement of the review topic with the Task Order Officer and the topic nominators (Table 2).We will include studies of women with primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum) postpartum hemorrhage (PPH) immediately post-birth to 12 weeks postpartum following pregnancy >24 weeks' gestation and include all birth settings (hospital, birth center, home). We will limit the search to studies conducted in very high human development countries[43] comparable to the U.S. and conducted from 1990 to the present. We selected this date to reflect current standards of care for PPH. Interventions such as the B-Lynch suture were introduced in the late 1990s,[44] and embolization techniques were not widely used until the mid- to late-1990s.[45, 46] Misoprostol was initially used as a treatment for gastric ulcer and not broadly used for PPH prevention or treatment until the 2000s. The World Health Organization recommended its use for prevention of PPH in 2007.[47, 48] Given that currently used interventions were not in widespread use prior to 1990, we set 1990 as a conservative lower bound for the search.

We will include studies published in English only. Two team members independently reviewed the titles and abstracts of the non-English language literature published since

1990 and located via our MEDLINE search. We determined that the majority would not meet our review criteria. Given the high percentage of non-eligible items in this scan (90%), we feel that excluding non-English studies will not introduce significant bias into the review. We will, however, re-assess non-English studies as we update our MEDLINE search. The team will evaluate any additional non-English studies that appear relevant to determine how or if these studies should be addressed in the review (e.g., appendix providing relevant information gleaned from abstract).

We will not require a minimum sample size for comparative studies addressing Key Questions 1-4. We considered the following factors in this decision:

- Comparative effectiveness studies could include preventive and treatment interventions or treatment interventions only. The former would have a PPH prevalence less than 100 percent, whereas 100 percent of participants in the latter type would have PPH. Loss to follow-up should be minimal for effectiveness studies.
- We set Type I error, alpha level, or p value at a standard at 0.05 and desired statistical power level at 0.80. For estimating sample size, we used the one-tailed z-test and the t-test.
- Using the above information, and the possibility of an effect size for continuous outcomes as large as 0.80 or more, the smallest sample size that could yield significant results would be an N of 42. For an outcome such as death, a study with an N of less than 20 could be adequate to show statistical significance.
- In the event that two or more studies have similar enrollment criteria and populations, and use the same intervention and comparator, meta-analysis could be possible. If meta-analysis is done, then studies with an N smaller than 42 could be combined.

Therefore, we did not set exclusion criteria for study size at the data extraction stage. This means that some studies may be included for initial consideration and later found not to be useable in a meta-analysis or also to be too small to contribute meaningful evidence.

We will include population-based case series or registry studies (e.g., studies reporting data from an entire state, country, or region) including at least 50 cases of PPH treatment for KQ 1-4 as we anticipate few comparative studies addressing these questions. While subject to greater risk of bias, including these population-based studies, with appropriate caveats about potential bias, should allow us to present a fuller picture of PPH treatment. We will also include case series reporting on at least 50 cases of PPH treatment for KQ3. Because of the numerous possible harm outcomes and study designs, we were not able to determine a specific sample size that would be suitable for finding statistically significant evidence of harm (or absence of harm); thus, we set a conservative limit that balances the need for smaller studies of specialized populations with the need for studies with sample sizes large enough to measure effects of the intervention.

We will include pre-post studies and other comparative studies of any size and addressing systems-level approaches for KQ5; these studies must explicitly state, as a primary or secondary aim, that they are assessing effects of a systems-level intervention on PPH management. Each study's analytic models must include data analyses of the effect of the strategy as it relates to PPH treatment, and results data must include information about effects of strategies on management of PPH. Further, studies'

discussion sections must interpret the strategy as potentially having value/not having value for PPH management.

As none of the recently published reviews of PPH treatment we identified in our preliminary scan of the literature addressed treatments comprehensively, we will use recent systematic reviews and meta-analyses as a source of references and to put the findings of our review in context.

Table 2. Inclusion Criteria

Category	Criteria
Study population	• KQ1-3, 5: Women with postpartum hemorrhage (PPH) immediately post-birth to 12 weeks postpartum following pregnancy >24 weeks' gestation • KQ4: Women with stabilized PPH and acute blood loss anemia • All modes of birth in any setting
Time period	1990 to present
Publication languages	English only
Country	Very High Human Development countries as indicated by the United Nations Development Programme Human Development Index. Countries as of April 2014 include: Norway, Australia, US, Netherlands, Germany, New Zealand, Ireland, Sweden, Switzerland, Japan, Canada, Republic of Korea, Hong Kong, Iceland, Denmark, Israel, Belgium, Austria, Singapore, France, Finland, Slovenia, Spain, Liechtenstein, Italy, Luxembourg, UK, Czech Republic, Greece, Brunei Darussalam, Cyprus, Malta, Andorra, Estonia, Slovakia, Qatar, Hungary, Barbados, Poland, Chile, Lithuania, United Arab Emirates, Portugal, Latvia, Argentina, Seychelles, and Croatia

Admissible evidence (study design and other criteria)	Admissible designs
	• KQ 1-2, 4: RCT or prospective/ retrospective cohort studies, population-based case series or registry studies with ≥50 cases of PPH treatment
	• KQ 3: RCT or prospective/ retrospective cohort studies, case series with ≥50 cases
	• KQ 5: Pre- and post-studies related to large-scale health systems changes, RCTs, prospective/retrospective cohort studies
	
	Other criteria
	• Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results
	• Studies targeting women with postpartum hemorrhage and meet the population criteria as described above
	• Studies that address:
	  ○ Treatment modality aimed at treatment/management of postpartum hemorrhage in a relevant population or treatment for acute blood loss anemia following stabilization of PPH
	  ○ Outcomes related to interventions; primary outcomes of interest include blood loss, transfusion, ICU admission, anemia, length of stay, mortality, uterine preservation, future fertility, breastfeeding, and psychological impact, and harms.
	• Studies must include extractable data presented in text or tables (vs. solely in figures) on relevant outcomes; we will contact authors for such data for those studies that we deem to be of low risk of bias and able to affect conclusions
	• For KQ 5, studies must explicitly assess effects of an systems-level intervention on PPH management as a primary or secondary aim; analytic models must indicate data analysis of the effect of the strategy as it relates to PPH treatment; results data include information about effects of strategy on management of PPH; discussion interprets the strategy as potentially having value/not having value for PPH management

Abbreviations: KQ=key question; ICU=Intensive Care Unit; RCT=randomized controlled trial

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B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Search strategies and databases

We conducted a targeted scan of the literature to identify the general scope of the primary literature. The initial search was focused on interventions used in the management of PPH.

We anticipate using the search strategy in Appendix A, adapted as needed for each database. We will limit the final search to 1990 to present to capture literature relevant to current clinical practice. Interventions such as the B-Lynch suture were introduced in the late 1990s,[44] and embolization techniques were not widely used until the mid- to late-1990s.[45, 46] Misoprostol was initially used as a treatment for gastric ulcer and not broadly used for PPH prevention or treatment until the 2000s. The World Health Organization recommended its use for prevention of PPH in 2007[47, 48] Given that currently used interventions were not in widespread use prior to 1990, we set 1990 as a conservative lower bound for the search.

Databases. To ensure comprehensive retrieval of relevant studies, we will use the following key databases: the MEDLINE medical literature database via the PubMed interface, EMBASE, and the Cumulative Index to Nursing and Allied Health (CINAHL). We will test the POPLINE database to determine whether it provides additional intervention or harms data. As noted, we anticipate using the search strategy in Table 2, adapted as needed for each database.

Hand searching. We will carry out hand searches of the reference lists of recent, relevant systematic reviews and comprehensive narrative reviews; the investigative team will also scan the reference lists of articles that are included after the full-text review phase for studies that potentially could meet inclusion criteria.

Search updates. We will update the literature search while the report is undergoing peer review and will add any studies meeting our inclusion criteria.

Grey literature. We have requested Scientific Information Packets and regulatory information addressing medications with FDA-approval for postpartum hemorrhage including oxytocin (Pitocin®), Prostaglandin E1/misoprostol (Cytotec®), methylergonovine (Methergine®), prostaglandin 15-methyl $F_{2\alpha}$/carboprost tromethamine (Hemabate®), prostaglandin E2/dinoprostone(Cervidil® or Prepidil®), NovoSeven®, and Cyklokapron®; and devices for postpartum hemorrhage including Bakri™ postpartum balloon, non-pneumatic anti-shock garment (NASG), Foley catheter, Sengstaken-Blakemore tube, and the Rusch balloon.

We will review citations provided via these searches against our criteria for potential inclusion.

C. Data Abstraction and Data Management

Screening and extraction forms

We will develop data collection forms for abstract review, full-text review, and data extraction. The abstract review form will contain questions about the primary exclusion

and inclusion criteria for initial screening. The full-text screening form will be used to examine the full text of papers that met initial criteria for inclusion in abstract review. Data extraction forms will collect those data necessary to create evidence tables and perform data synthesis. After reviewing a sample of relevant articles, the team will test and revise the screening and data collection forms before beginning each stage of screening or data extraction.

Initial review of abstracts

We will review all the titles and abstracts retrieved by the searches against pre-established inclusion and exclusion criteria. Two team members will independently review each abstract. Both reviewers must agree to exclude an abstract. We will promote abstracts for full-text review when one or both reviewers determine that the abstract meets criteria for inclusion. Abstracts with insufficient information will be promoted for full-text review.

Retrieving and reviewing articles

We will retrieve and review the full-text from all abstracts screened for inclusion and abstracts for which we were unable to make a decision about eligibility. Each article will be reviewed by at least two members of the investigative team. Disagreements between the reviewers will be adjudicated by the lead investigator or via investigative team consensus. We will use a simple categorization scheme to code the reasons for exclusion for papers that are not included in the report. We will record the exclusion reasons using prespecified codes in an EndNote® (Thomson Reuters, New York, NY) bibliographic database so that we can compile the list of excluded articles with exclusion reasons.

Data extraction

For studies that meet the conditions of the full text review assessment, we will record study characteristics (i.e., study design, year, location, randomization, intervention characteristics, and related publications). We will also extract key data and study quality elements for each study in the System Review Data Repository (SRDR) system.

We anticipate that these data will include study participant characteristics (e.g., age, race/ethnicity, parity, etc.), intervention characteristics (e.g., who provided the intervention, components of the intervention, and where the intervention was provided), and outcomes.

We will extract at minimum the information outlined in Table 3 from included studies when reported. A second reviewer will review the data extraction against the original articles for quality control. Differences in data coding between the abstractor and the reviewer will be resolved by consensus.

Table 3. Population/intervention characteristics and outcomes of interest

KQ	Characteristics	Intermediate Outcomes	Final Outcomes
1a-1d	• Maternal age, PPH risk factors, parity • Primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum) • Severity of PPH (as reported in each study) • Mode of birth • Use and timing of: – Compression techniques (external uterine massage, bimanual compression, aortic compression) – Medications – Procedures (manual removal of placenta, manual evacuation of clot, uterine tamponade, uterine artery embolization, laceration repair) – Surgeries (curettage, uterine artery ligation, uterine hemostatic compression suturing, hysterectomy) – Blood and fluid products – Anti-shock garment • Birth setting • Facility characteristics	• Blood loss • Transfusion • ICU admission • Anemia • Length of stay	• Mortality • Uterine preservation • Future fertility • Breastfeeding • Psychological impact • Harms of intervention
2	• Maternal age, PPH risk factors, parity • Primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum) • Severity of PPH (as reported in each study) • Mode of birth • Use and timing of: – Compression techniques (external uterine massage, bimanual compression, aortic compression) – Medications – Procedures (manual removal of placenta, manual evacuation of clot, uterine tamponade, uterine artery embolization, laceration repair) – Surgeries (curettage, uterine artery ligation, uterine hemostatic compression suturing, hysterectomy) – Blood and fluid products – Anti-shock garment • Birth setting • Facility characteristics	• Blood loss • Transfusion • ICU admission • Anemia • Length of stay	• Mortality • Uterine preservation • Future fertility • Breastfeeding • Psychological impact • Harms of intervention

Table 3. Population/intervention characteristics and outcomes of interest, continued

KQ	Characteristics	Intermediate Outcomes	Final Outcomes
3	• Maternal age, PPH risk factors, parity • Primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum) • Severity of PPH (as reported in each study) • Mode of birth • Use and timing of: – Compression techniques (external uterine massage, bimanual compression, aortic compression) – Medications – Procedures (manual removal of placenta, manual evacuation of clot, uterine tamponade, uterine artery embolization, laceration repair) – Surgeries (curettage, uterine artery ligation, uterine hemostatic compression suturing, hysterectomy) – Blood and fluid products – Anti-shock garment • Birth setting • Facility characteristics	• Blood loss	• Mortality • Loss of fertility • adverse effects
4	• Maternal age, PPH risk factors, parity • Primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum) • Severity of PPH (as reported in each study) • Mode of birth • Use and timing of: – Compression techniques (external uterine massage, bimanual compression, aortic compression) – Medications – Procedures (manual removal of placenta, manual evacuation of clot, uterine tamponade, uterine artery embolization, laceration repair) – Surgeries (curettage, uterine artery ligation, uterine hemostatic compression suturing, hysterectomy) – Blood and fluid products – Anti-shock garment • Birth setting • Facility characteristics • F/u procedures	• Blood loss • Transfusion • ICU admission • Anemia • Length of stay	• Mortality • Resolution of anemia • Psychological impact • Harms of intervention

Table 3. Population/intervention characteristics and outcomes of interest

KQ	Characteristics	Intermediate Outcomes	Final Outcomes
5	• Maternal age, PPH risk factors, parity • Primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum) • Severity of PPH (as reported in each study) • Mode of birth • Description of systems-level intervention • Use and timing of: – Compression techniques (external uterine massage, bimanual compression, aortic compression) – Medications – Procedures (manual removal of placenta, manual evacuation of clot, uterine tamponade, uterine artery embolization, laceration repair) – Surgeries (curettage, uterine artery ligation, uterine hemostatic compression suturing, hysterectomy) – Blood and fluid products – Anti-shock garment • Birth setting • Facility characteristics	• Blood loss • Transfusion • ICU admission • Anemia • Length of stay • Harms of intervention	• Mortality • Uterine preservation • Future fertility • Breastfeeding • Psychological impact

Abbreviations: NA=not applicable; NICU=Neonatal Intensive Care Unit

Evidence tables

We will extract data into SRDR using predetermined abbreviations and acronyms consistently across all entries. The areas of special focus for data extraction may vary by KQ as appropriate, but we will extract common elements, such as author, year of publication, study location and time period, population description, sample size, study type, intervention(s) and comparator(s), population characteristics, baseline data, and outcomes.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess the quality of studies for the outcomes specified in Table 3 using criteria from established tools and the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[49] We will assess quality for those outcomes reported in at least one randomized study or three observational studies. We will use the Cochrane Risk of Bias tool[50] for randomized controlled trials and the Newcastle-Ottawa scale[51] for cohort studies. We will use the McMaster Quality Assessment Scale of Harms (McHarm) tool to assess harms studies.[52] We will describe study quality as "good," "fair," or "poor" using pre-established thresholds for the risk of bias assessments. Two senior investigators will independently assess each included study. Disagreements between assessors will be resolved through discussion. We will report findings of poor quality studies in evidence tables but will focus our analyses on those studies with lower risk of bias, i.e., studies of good or fair quality as determined in our quality assessment process

E. Data Synthesis

Synthesizing results

We anticipate variations in the populations and interventions studied that may preclude meta-analysis. We will work with our statistician to determine whether a quantitative analysis can be performed by considering such factors as the number of studies addressing an outcome/intervention, population and intervention characteristics, completeness of reporting of the results, and consistency of results. We will provide a qualitative synthesis of studies meeting our review criteria.

Where possible, we will discuss results for subgroups (e.g., defined by etiology of PPH, treatment type [medical or surgical], PPH severity or timing) as reported in the studies meeting our criteria. Studies may report differences in outcome by timing of intervention, etiology, or setting, and we will capture those data and stratify our presentation of results as much as possible.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will use explicit criteria for rating the overall strength of the evidence (SOE) for the outcomes specified in Table 3. We will rate the SOE for key outcomes of relevance to patients. We consider the following outcomes as important to patients, based on the Patient Centered Outcomes Research Institute definition of patient-centered outcomes as of relevance to survival, function, symptoms, and health related quality of life and the definition used in the Strength of Recommendation Taxonomy[53]: mortality, uterine preservation, transfusion, ICU admission, future fertility, breastfeeding, psychological impact, and harms of intervention.

We will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge. We will make these judgments as appropriate for each of the KQs.

The strength of evidence evaluation will be that stipulated in the Effective Health Care Program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews,*[49] which emphasizes the following five major domains: study limitations (low, medium, high), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), precision (precise, imprecise), and reporting bias (present, undetected). Study limitations are derived from the quality assessment of the individual studies that addressed the KQ and specific outcome under consideration. Each key outcome on each comparison of interest will be given an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence will be graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect), "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate), "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate), or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect).

When no studies are available for an outcome or comparison of interest, we will grade the evidence as insufficient.

Two senior staff will independently grade the body of evidence; disagreements will be resolved as needed through discussion or third-party adjudication. We will record strength of evidence assessments in tables, summarizing for each outcome.

G. Assessing Applicability

We will assess the applicability of findings reported in the included literature to the general population of women experiencing PPH by determining the PICOS (**p**opulation, **i**ntervention, **c**omparator, **o**utcomes, and **s**etting) in each study and developing an overview of these elements for each intervention category. We anticipate variation in the scope of interventions offered by PPH etiology, area of the country, timing of PPH (primary versus secondary), provider characteristics, and birth setting (home, birth center, or hospital) and facility characteristics (tertiary care hospitals, community hospitals, etc.).

V. References

1. Rath WH. Postpartum hemorrhage--update on problems of definitions and diagnosis. Acta Obstet Gynecol Scand 2011 May;90(5):421-8. PMID: 21332452.
2. Kavle JA, Khalfan SS, Stoltzfus RJ, et al. Measurement of blood loss at childbirth and postpartum. Int J Gynaecol Obstet 2006 Oct;95(1):24-8. PMID: 16919628.
3. Stafford I, Dildy GA, Clark SL, et al. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol 2008 Nov;199(5):519 e1-7. PMID: 18639209.
4. Schorn MN. Measurement of blood loss: review of the literature. J Midwifery Womens Health 2010 Jan-Feb;55(1):20-7. PMID: 20129226.
5. Carroli G, Cuesta C, Abalos E, et al. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol 2008 Dec;22(6):999-1012. PMID: 18819848.
6. Calvert C, Thomas SL, Ronsmans C, et al. Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis. PLoS One 2012;7(7):e41114. PMID: 22844432.
7. Ford JB, Roberts CL, Simpson JM, et al. Increased postpartum hemorrhage rates in Australia. Int J Gynaecol Obstet 2007 Sep;98(3):237-43. PMID: 17482190.
8. Joseph KS, Rouleau J, Kramer MS, et al. Investigation of an increase in postpartum haemorrhage in Canada. BJOG 2007 Jun;114(6):751-9. PMID: 17516968.
9. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC Pregnancy Childbirth 2009;9:55. PMID: 19943928.
10. Lutomski JE, Byrne BM, Devane D, et al. Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study. BJOG 2012 Feb;119(3):306-14. PMID: 22168794.
11. Mehrabadi A, Hutcheon J, Lee L, et al. Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-based retrospective cohort study. BJOG 2013 Jun;120(7):853-62. PMID: 23464351.
12. Mehrabadi A, Hutcheon JA, Lee L, et al. Trends in postpartum hemorrhage from 2000 to 2009: a population-based study. BMC Pregnancy Childbirth 2012;12:108. PMID: 23057683.
13. Rossen J, Okland I, Nilsen OB, et al. Is there an increase of postpartum hemorrhage, and is severe hemorrhage associated with more frequent use of obstetric interventions? Acta Obstet Gynecol Scand 2010 Oct;89(10):1248-55. PMID: 20809871.
14. Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994-2006. Am J Obstet Gynecol 2010 Apr;202(4):353 e1-6. PMID: 20350642.
15. World Health Organization. WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. Geneva: World Health Organization.; 2012.
16. Berg CJ, Harper MA, Atkinson SM, et al. Preventability of pregnancy-related deaths: results of a state-wide review. Obstet Gynecol 2005 Dec;106(6):1228-34. PMID: 16319245.
17. Kilpatrick SJ, Prentice P, Jones RL, et al. Reducing maternal deaths through state maternal mortality review. J Womens Health (Larchmt) 2012 Sep;21(9):905-9. PMID: 22621323.

18. Della Torre M, Kilpatrick SJ, Hibbard JU, et al. Assessing preventability for obstetric hemorrhage. Am J Perinatol 2011 Dec;28(10):753-60. PMID: 21698554.
19. McLintock C, James AH. Obstetric hemorrhage. J Thromb Haemost 2011 Aug;9(8):1441-51. PMID: 21668737.
20. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. Obstet Gynecol 2006 Oct;108(4):1039-47. PMID: 17012482.
21. Zelop CM. Postpartum hemorrhage: becoming more evidence-based. Obstet Gynecol 2011 Jan;117(1):3-5. PMID: 21173639.
22. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage: No. 235 October 2009 (Replaces No. 88, April 2000). Int J Gynaecol Obstet 2010 Mar;108(3):258-67. PMID: 20196196.
23. Royal College of Obstetricians and Gynaecologists. Prevention and management of postpartum haemorrhage. RCOG Green-top Guideline No. 52. London: Royal College of Obstetricians and Gynaecologists; 2009.Available from http://www.rcog.org.uk/womens-health/clinical-guidance/prevention-and-management-postpartum-haemorrhage-green-top-52
24. International joint policy statement. FIGO/ICM global initiative to prevent post-partum hemorrhage. J Obstet Gynaecol Can 2004 Dec;26(12):1100-2, 8-11. PMID: 15696639.
25. Lalonde A. Prevention and treatment of postpartum hemorrhage in low-resource settings. Int J Gynaecol Obstet 2012 May;117(2):108-18. PMID: 22502595.
26. Miller S, Ojengbede O, Turan JM, et al. A comparative study of the non-pneumatic anti-shock garment for the treatment of obstetric hemorrhage in Nigeria. Int J Gynaecol Obstet 2009 Nov;107(2):121-5. PMID: 19628207.
27. Miller S, Fathalla MM, Youssif MM, et al. A comparative study of the non-pneumatic anti-shock garment for the treatment of obstetric hemorrhage in Egypt. Int J Gynaecol Obstet 2010 Apr;109(1):20-4. PMID: 20096836.
28. Franchini M, Franchi M, Bergamini V, et al. The use of recombinant activated FVII in postpartum hemorrhage. Clin Obstet Gynecol 2010 Mar;53(1):219-27. PMID: 20142658.
29. Soltan MH, Faragallah MF, Mosabah MH, et al. External aortic compression device: the first aid for postpartum hemorrhage control. J Obstet Gynaecol Res 2009 Jun;35(3):453-8. PMID: 19527382.
30. Keogh J, Tsokos N. Aortic compression in massive postpartum haemorrhage--an old but lifesaving technique. Aust N Z J Obstet Gynaecol 1997 May;37(2):237-8. PMID: 9222477.
31. Haeri S, Dildy GA, 3rd. Maternal mortality from hemorrhage. Semin Perinatol 2012 Feb;36(1):48-55. PMID: 22280866.
32. Skupski DW, Lowenwirt IP, Weinbaum FI, et al. Improving hospital systems for the care of women with major obstetric hemorrhage. Obstet Gynecol 2006 May;107(5):977-83. PMID: 16648399.
33. Rizvi F, Mackey R, Barrett T, et al. Successful reduction of massive postpartum haemorrhage by use of guidelines and staff education. BJOG 2004 May;111(5):495-8. PMID: 15104617.

34. Audureau E, Deneux-Tharaux C, Lefevre P, et al. Practices for prevention, diagnosis and management of postpartum haemorrhage: impact of a regional multifaceted intervention. BJOG 2009 Sep;116(10):1325-33. PMID: 19538416.
35. Deneux-Tharaux C, Dupont C, Colin C, et al. Multifaceted intervention to decrease the rate of severe postpartum haemorrhage: the PITHAGORE6 cluster-randomised controlled trial. BJOG 2010 Sep;117(10):1278-87. PMID: 20573150.
36. Dupont C, Touzet S, Colin C, et al. Incidence and management of postpartum haemorrhage following the dissemination of guidelines in a network of 16 maternity units in France. Int J Obstet Anesth 2009 Oct;18(4):320-7. PMID: 19733052.
37. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev 2007(1):CD003249. PMID: 17253486.
38. Alexander J, Thomas P, Sanghera J. Treatments for secondary postpartum haemorrhage. Cochrane Database Syst Rev 2002(1):CD002867. PMID: 11869640.
39. Tindell K, Garfinkel R, Abu-Haydar E, et al. Uterine balloon tamponade for the treatment of postpartum haemorrhage in resource-poor settings: a systematic review. BJOG 2013 Jan;120(1):5-14. PMID: 22882240.
40. Rossi AC, Lee RH, Chmait RH. Emergency postpartum hysterectomy for uncontrolled postpartum bleeding: a systematic review. Obstet Gynecol 2010 Mar;115(3):637-44. PMID: 20177297.
41. Ferrer P, Roberts I, Sydenham E, et al. Anti-fibrinolytic agents in post partum haemorrhage: a systematic review. BMC Pregnancy Childbirth 2009;9:29. PMID: 19604358.
42. Gizzo S, Saccardi C, Patrelli TS, et al. Fertility rate and subsequent pregnancy outcomes after conservative surgical techniques in postpartum hemorrhage: 15 years of literature. Fertil Steril 2013 Jun;99(7):2097-107. PMID: 23498891.
43. United Nations Human Development Programme. United Nations Human Development Reports: Human Development Index (HDI). Available from: http://hdr.undp.org/en/statistics/hdi.
44. Matsubara S, Yano H, Ohkuchi A, et al. Uterine compression sutures for postpartum hemorrhage: an overview. Acta Obstet Gynecol Scand 2013 Apr;92(4):378-85. PMID: 23330882.
45. Merland JJ, Houdart E, Herbreteau D, et al. Place of emergency arterial embolisation in obstetric haemorrhage about 16 personal cases. Eur J Obstet Gynecol Reprod Biol 1996 Mar;65(1):141-3. PMID: 8706947.
46. Kim TH, Lee HH, Kim JM, et al. Uterine artery embolization for primary postpartum hemorrhage. Iran J Reprod Med 2013 Jun;11(6):511-8. PMID: 24639786.
47. Hofmeyr GJ, Gulmezoglu AM, Novikova N, et al. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organ 2009 Sep;87(9):666-77. PMID: 19784446.
48. World Health Organization. WHO recommendations for the prevention of postpartum haemorrhage. WHO. Geneva: 2007. Available from: http://whqlibdoc.who.int/hq/2007/WHO_MPS_07.06_eng.pdf
49. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012 . Chapters available at: www.effectivehealthcare.ahrq.gov.

50. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. PMID: 22008217.
51. Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
52. McMaster Quality Assessment Scale of Harms (McHarm) for primary studies. Hamilton ON, McMaster University 2008.
53. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. J Am Board Fam Pract 2004 Jan-Feb;17(1):59-67. PMID: 15014055.

VI. Acronyms and Abbreviations

ACOG: American College of Obstetricians and Gynecologists
AF: Analytic Framework
CER: Comparative Effectiveness Review
CINAHL: Cumulative Index to Nursing and Allied Health
D&C: Dilation and Curettage
EPC: Evidence-based Practice Center
FDA: Food and Drug Administration
FIGO: International Federation of Gynecologists and Obstetricians
ICM: International Confederation of Midwives
ICU: Intensive Care Unit
KQ: Key Question
PICOTS: Population, Intervention, Comparators, Outcomes, Timing, Setting
PPH: Postpartum Hemorrhage
RCOG: Royal College of Obstetricians and Gynaecologists
SOE: Strength of the evidence
SIP: Scientific Information Packets
WHO: World Health Organization

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	*Section*	*Original Protocol*	*Revised Protocol*	*Rationale*
This should be the effective date of the change in protocol	*Specify where the change would be found in the protocol*	*Describe the language of the original protocol.*	*Describe the change in protocol.*	*Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.*

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA 29020120009I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Preliminary Search Strategies

Table A-1. Preliminary MEDLINE search strategy

Search terms		Results
#1	"postpartum hemorrhage"[MeSH Terms] OR "postpartum hemorrhage"[tiab] OR "postpartum haemorrhage"[tiab] OR (PPH[tiab] AND postpartum[tiab]) OR "obstetric hemorrhage"[tiab] OR "obstetric haemorrhage"[tiab] OR (("postpartum period"[MeSH Terms] OR post-partum[tiab]) AND ("hemorrhage"[MeSH Terms] OR hemorrhage[tiab] OR haemorrhage[tiab]))	7128
#2	management[tiab] OR therapy[tiab] OR "Therapeutics"[Mesh:NoExp] OR treatment[tiab] OR "fundal massage"[tiab] OR "uterine massage"[tiab] OR ((fundus[tiab] OR fundal[tiab] OR uterus[tiab] OR "uterus"[MeSH Terms] OR uterine[tiab]) AND (massage[tiab] OR "massage"[MeSH Terms])) OR compression[tiab] OR "antishock garment"[tiab] OR "antishock garments"[tiab] OR "Gravity Suits"[MeSH Terms] OR "Fluid Therapy"[mh] OR uterotonic[tiab] OR oxytocin[tiab] OR "oxytocin"[MeSH Terms] OR Pitocin[tiab] OR oxytoxic[tiab] OR Oxytocics[mesh] OR misoprostol[tiab] OR "misoprostol"[MeSH Terms] OR Cytotec[tiab] OR methylergonovine[tiab] OR "methylergonovine"[MeSH Terms] OR methergine[tiab] OR ergonovine[tiab] OR "ergonovine"[MeSH Terms] OR ergotrate[tiab] OR "Ergot Alkaloids"[mh] OR ergot[tiab] OR ergometrine[tiab] OR carboprost[tiab] OR "carboprost"[MeSH Terms] OR "carboprost tromethamine"[Supplementary Concept] OR "PGE1"[tiab] OR hemabate[tiab] OR transfusion[tiab] OR "Blood Transfusion"[mh] OR "fluid resuscitation"[tiab] OR "isotonic crystalloids"[tiab] OR "isotonic crystalloid"[tiab] OR "crystalloid solutions"[Supplementary Concept] OR "Ringer's Lactate"[tiab] OR "lactated ringer's"[tiab] OR "Ringer's lactate"[Supplementary Concept] OR "isotonic saline"[tiab] OR "blood products"[tiab] OR "volume replacement"[tiab] OR fibrinogen[tiab] OR "fibrinogen"[MeSH Terms] OR "fresh frozen plasma"[tiab] OR "plasma"[MeSH Terms] OR "packed cells"[tiab] OR cryoprecipitate[tiab] OR "uterine tamponade"[tiab] OR "balloon tamponade"[tiab] OR "intrauterine balloon"[tiab] OR "uterine balloon"[tiab] OR "Uterine Balloon Tamponade"[mh] OR "Bakri balloon"[tiab] OR ((uterus[tiab] OR "uterus"[MeSH Terms] OR uterine[tiab] OR intrauterine[tiab]) AND pack*[tiab]) OR "Bakri balloon"[tiab] OR "arterial embolization"[tiab] OR "artery embolization"[tiab] OR "Embolization, Therapeutic"[mh] OR "artery ligation"[tiab] OR "ligation"[MeSH Terms] OR "arterial ligation"[tiab] OR "laceration repair"[tiab] OR "recombinant activated factor VII"[tiab] OR "rFVIIa"[tiab] OR "Factor VIIa"[mh] OR Laparotomy[tiab] OR "laparotomy"[MeSH Terms] OR Hysterectomy[tiab] OR "hysterectomy"[MeSH Terms] OR "B-lynch"[tiab] OR "Suture Techniques"[MeSH Terms] OR suture[tiab] OR suturing[tiab] OR "Uterine Inertia/prevention and control"[Mesh] OR "Uterine Inertia/therapy"[Mesh] OR "Uterine Inversion/therapy"[Mesh] OR "Uterine Rupture/therapy"[Mesh] OR "Dilatation and Curettage"[MeSH Terms] OR curettage[tiab] OR "uterine exploration"[tiab] OR "urinary catheterization"[tiab] OR "Urinary Catheterization"[Mesh] OR "catheter balloon"[tiab] OR "balloon catheter"[tiab] OR "foley catheter"[tiab] OR "condom catheter"[tiab] OR "condom tamponade"[tiab] OR (Condoms[Mesh] AND balloon[tiab]) OR "Rusch balloon"[tiab] OR "Sengstaken-Blakemore"[tiab] OR ("manual removal"[tiab] AND placenta[tiab]) OR "Placenta, Retained/therapy"[Mesh] OR "Resource Allocation"[Mesh] OR "Delivery of Health Care"[Mesh:NoExp] OR "Program Development"[Mesh] OR "Critical Pathways"[Mesh] OR "Guideline Adherence"[Mesh] OR "Clinical Protocols"[Mesh] OR "Algorithms"[Mesh] OR algorithm*[tiab] OR protocol*[tiab] OR system[tiab] OR systems[tiab] OR systemic*[tiab] OR "Patient Care	8820233

	Team/organization and administration"[Mesh] OR "Practice Guidelines as Topic"[Mesh] OR "Checklist"[Mesh] OR "adverse effects"[Subheading] OR unsafe[tiab] OR safety[tiab] OR harm[tiab] OR harms[tiab] OR harmful[tiab] OR complication[tiab] OR complications[tiab] OR "side-effect"[tiab] OR "side-effects"[tiab] OR ((undesirable OR adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)) OR sequelae[tiab] OR sequela[tiab] OR "Postoperative Complications"[Mesh] OR ((postoperative[tiab] OR surgical[tiab] OR postsurgical[tiab] OR "post operative"[tiab] OR "post surgical"[tiab]) AND (complication[tiab] OR complications[tiab])) OR "adverse effects"[Subheading] OR complications[Subheading] OR contraindications[Subheading]	
#3	#1 AND #2 AND English[lang]	4379
#4	newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR review[pt] OR practice guideline[pt] OR guideline[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR legal cases[pt] OR published erratum[pt] OR congresses[pt]	5019085
#5	#3 NOT #4	2729
#6	#5 AND ("1990/01/01"[PDAT] : "3000/12/31"[PDAT])	2124*

Key: [mh] Medical Subject Heading; [tiab] title/abstract word; [pt] publication type; [sh] subheading; [PDAT] publication date

*Note: numbers do not tally as some articles are excluded in more than one category