Evidence-based Practice Center Systematic Review Protocol

Project Title: Systematic Review Update of Venous Thromboembolism Prophylaxis in Orthopedic Surgery

I. Background and Objectives for the Systematic Review

Major orthopedic surgery describes three surgical procedures including total hip replacement, total knee replacement, and hip fracture surgery. As a whole, major orthopedic surgery carries a risk for venous thromboembolism (VTE)—deep vein thrombosis (DVT) and pulmonary embolism (PE). A variety of strategies to prevent VTE are available, including pharmacological (antiplatelet, anticoagulant) and mechanical modalities that can be used alone or in combination. However, prophylaxis with pharmacologic strategies also has risks including major bleeding, prosthetic joint infections, and the need for reoperation, but mechanical modalities (when used alone) are thought to be inferior to pharmacological agents to prevent VTE.

VTE prophylaxis (or "thromboprophylaxis) is now standard of care for patients undergoing major orthopedic surgery. Prophylaxis has been demonstrated to reduce the incidence of symptomatic and asymptomatic DVT (in comparison to placebo or no prophylaxis); however, because of rarity of postoperative PE, the body of randomized controlled trial (RCT) evidence is not adequately powered to demonstrate the effect of prophylaxis on PE. Nevertheless, the effect of prophylaxis on DVT risk reduction is generally considered an adequate proxy for likely PE risk reduction. Furthermore, avoiding DVT is a clinically worthwhile goal to reduce the incidence of lower extremity venous disease such as postphlebitic syndrome, venous insufficiency, and phlegmasia cerulean dolens (resulting in edema, pain, and gangrene).

The 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery[1] (hereafter "the 2012 report") addressed many of the uncertainties in this area, including questions regarding the natural history of VTE, predictors of VTE, and the likelihood that DVTs result in PE in patients undergoing total hip replacement, total knee replacement, or hip fracture surgery; the comparative efficacy of VTE prophylaxis strategies with no VTE prophylaxis, within and between classes of VTE prophylaxis modalities, and duration of VTE prophylaxis in patients undergoing these surgeries; and the efficacy of VTE prophylaxis in non-major orthopedic surgeries (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery). The 2012 report included studies published from 1980 through May 2011. It found a general dearth of evidence regarding important clinical outcomes (nonfatal PE, fatal PE, major bleeding, reoperation), but high strength of evidence that pharmacologic VTE prophylaxis reduces the risk of DVT compared to no VTE prophylaxis and increases the risk of minor bleeding. Comparisons of mechanical VTE prophylaxis versus no VTE prophylaxis did not provide strong evidence of reducing the risk of VTE, including specifically DVT. The comparisons of different classes of VTE prophylaxis modalities (e.g., different pharmacologic classes or pharmacologic versus mechanical

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VTE prophylaxis) provided neither adequate evidence for important clinical outcomes nor strong evidence for other outcomes, including DVT. There were few studies evaluating the new factor Xa inhibitors. In general, different interventions within classes were not statistically significantly different in their effects on DVT or bleeding. There was not strong evidence for other Key Questions.

In preparation for development of this protocol, we conducted a surveillance review of new studies potentially eligible to update all Key Questions from the 2012 report. We screened and extracted basic data from abstracts found in PubMed from January 2010 to 16 July 2015. We evaluated the number and characteristics of studies—including RCT, nonrandomized comparative studies, systematic reviews / meta-analyses, and network meta-analyses—of potentially relevant articles. The updated literature search yielded 617 citations. Using the 2012 report's eligibility criteria, 160 articles were of potential interest (based on information available in their abstracts). Of these, 48 are existing systematic reviews, 49 are RCTs, 19 are pooling studies (meta-analysis or otherwise) of previous published or unpublished trials, and 44 are nonrandomized comparative studies (with at least 750 participants per study). We used this information to help determine the scope of the systematic review update.

Upon discussion of the current state of the evidence with a panel of technical experts, we determined that a focused update of the 2012 AHRQ report would be of value. The panel included 10 members, including four orthopedic surgeons, two hematologists, one pulmonologist, one pharmacologist, one physical therapist, and one nurse practitioner. In brief, based on their input and the findings of the surveillance review, we decided to focus the update on comparisons between specific prophylaxis interventions; different classes of intervention; different doses, regimens, and treatment durations of interventions; different combinations of interventions; and different timing of starting prophylaxis (in relation to the time of surgery).

Several topics covered in the 2012 AHRQ report will not be updated. Key Questions related to "natural history" in patients not given thromboprophylaxis and incidence or predictors of VTE will not be updated. In the modern era, it is rare for patients to not have some form of thromboprophylaxis; therefore it is unlikely for there to be new evidence regarding these topics. For similar reasons, we will not update the Key Question comparing thromboprophylaxis to no thromboprophylaxis. We will also not update the Key Question that evaluates DVT as a proxy (or predictor) for PE, as no new evidence is expected. Finally, all questions related to orthopedic surgeries other than TKR, THR, and hip fracture surgery will not be updated, since only very limited new studies were found during the surveillance review; thus, conclusions and strength of evidence are unlikely to change compared to the 2012 report.

The objectives for the systematic review are to update the 2012 AHRQ focused on the comparative effectiveness (for VTE outcomes and harms) of different thromboprophylaxis interventions for patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery).

II. The Key Questions

With input from clinical experts, we have developed the following Key Questions and study eligibility criteria for the systematic review update. The Key Questions were revised based on public comments.

The following are the Key Questions to be addressed by the review:

Question 1 (update of original Key Question 5): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of thromboprophylaxis interventions on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Question 2 (update of original Key Question 6): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual thromboprophylaxis interventions within classes (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Question 3 (new Key Question based on original Key Question 8): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of different doses, regimens, or treatment durations of the same thromboprophylaxis interventions (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Question 4 (update of original Key Question 7 plus expansion): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Question 5 (new Key Question): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), based on network meta-analysis, what are the comparative effects of thromboprophylaxis interventions on deep vein thrombosis and, separately, major bleeding?

- **5.1** What are the comparative effects of different classes of thromboprophylaxis interventions?
- **5.2** What are the comparative effects of different individual thromboprophylaxis interventions?

Question 6 (new Key Question): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of starting pharmacologic thromboprophylaxis at different times (i.e., preoperative, intraoperative, postoperative) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

For each Key Question, the review will include the evidence for subgroup (subpopulation) differences in effect or adverse events. These subgroups will be based on

key potential modifiers, including at least age, race/ethnicity, functional status (including quality of life), comorbidities, prior history of abnormal surgical bleeding or bleeding disorder, prior medications (including antiplatelet drugs), and kidney function.

Eligibility Criteria

The preliminary eligibility criteria for an update are not substantially different than the criteria for the original AHRQ review. The main differences relate to dropping Key Questions related to placebo (no prophylaxis) study arms and the Key Questions (KQ) regarding non-major orthopedic procedures. Other changes relate to the new questions comparing doses, regimens, duration of intervention, and timing of initiation of prophylaxis. Some of the criteria were rephrased for clarity or completeness.

Populations (all KQs)

- Patients undergoing major orthopedic surgery
    - Total hip replacement
    - Total knee replacement
    - Hip fracture surgery
    - Exclude studies that combine analyses of hip and knee surgeries
- Modifying factors and subpopulations to be considered
    - Age
    - Race/ethnicity
    - Health status
    - Comorbidities
    - Prior history of abnormal surgical bleeding or bleeding disorder
    - Prior medications (especially antiplatelet drugs)
    - Kidney function
    - Treatment adherence/compliance

Interventions

- Pharmacologic VTE prophylaxis agents within the defined classes:
    - Oral antiplatelet agents — KQ 1, 4 (in combination), 5, 6
    - Injectable low molecular weight heparin — All KQ
    - Injectable unfractionated heparin — KQ 1, 4 (in combination), 5, 6
    - Injectable or oral factor Xa inhibitors — All KQ
    - Injectable or oral direct thrombin inhibitors — All KQ
    - Oral vitamin K antagonists — KQ 1, 4 (in combination), 5, 6
- Mechanical VTE prophylaxis devices within the defined classes:
    - Graduated compression stockings — KQ 1 to 5
    - Intermittent pneumatic compression devices — KQ 1 to 5
    - Venous foot pumps — KQ 1 to 5
- Prophylactic interior vena cava filter placement — KQ 1, 5
- Multimodality/Combined treatment protocols (e.g., changes in modality, drug + mechanical) — KQ 1, 4, 5, 6

Comparators

- KQ 1 Intervention in different class
- KQ 2 Intervention within the same class
- KQ 3 Same intervention, different (lower) dose (or anticoagulation goal), (less intensive) regimen, or (shorter) duration of intervention
- KQ 4 Single modality intervention
- KQ 5 All agents are mutually interventions and comparators; include placebo or no VTE prophylaxis
- KQ 6 Same intervention started at different (later) time relative to surgery

Outcomes (KQ 1-4, 6; KQ 5 as noted)

- Final health or patient-centered outcomes
  - Total VTE (combined PE and DVT; symptomatic and asymptomatic)
  - Symptomatic VTE (combined PE and DVT)
  - PE
    - Total PE (fatal and nonfatal; symptomatic and asymptomatic)
    - Fatal PE
    - Symptomatic PE
  - Postthrombotic syndrome (PTS)
  - Pulmonary hypertension (due to PE)
- Intermediate outcomes (DVT may also be a final, patient-centered outcome)
  - DVT
    - Total DVT (symptomatic, asymptomatic; proximal, distal) *KQ 5 also*
    - Symptomatic DVT
    - Proximal DVT
  - Adherence (compliance) with treatment
- Adverse events due to intervention(s)
  - Major bleeding, total (*KQ 5 also*), including:
    - Fatal bleeding
    - Bleeding leading to transfusion
    - Major bleeding leading to reoperation
    - Major bleeding leading to readmission
    - Surgical site / joint bleeding
    - Bleeding leading to infection
    - As defined by authors
  - Surgical site/wound-related infections
  - Surgical site/wound complications (other than bleeding, infection)
  - Heparin-induced thrombocytopenia
  - Adverse events due to mechanical devices (as reported by authors)
  - Adverse events due to IVC filter (as reported by authors)
  - Other clinically significant adverse events reported by studies

Study design

- Randomized controlled trials (any study size) (*KQ 1-6)*
- Nonrandomized comparative observational studies (N ≥750 total per study) (*KQ 1-4, 6*)

Timing

- Any duration of follow-up

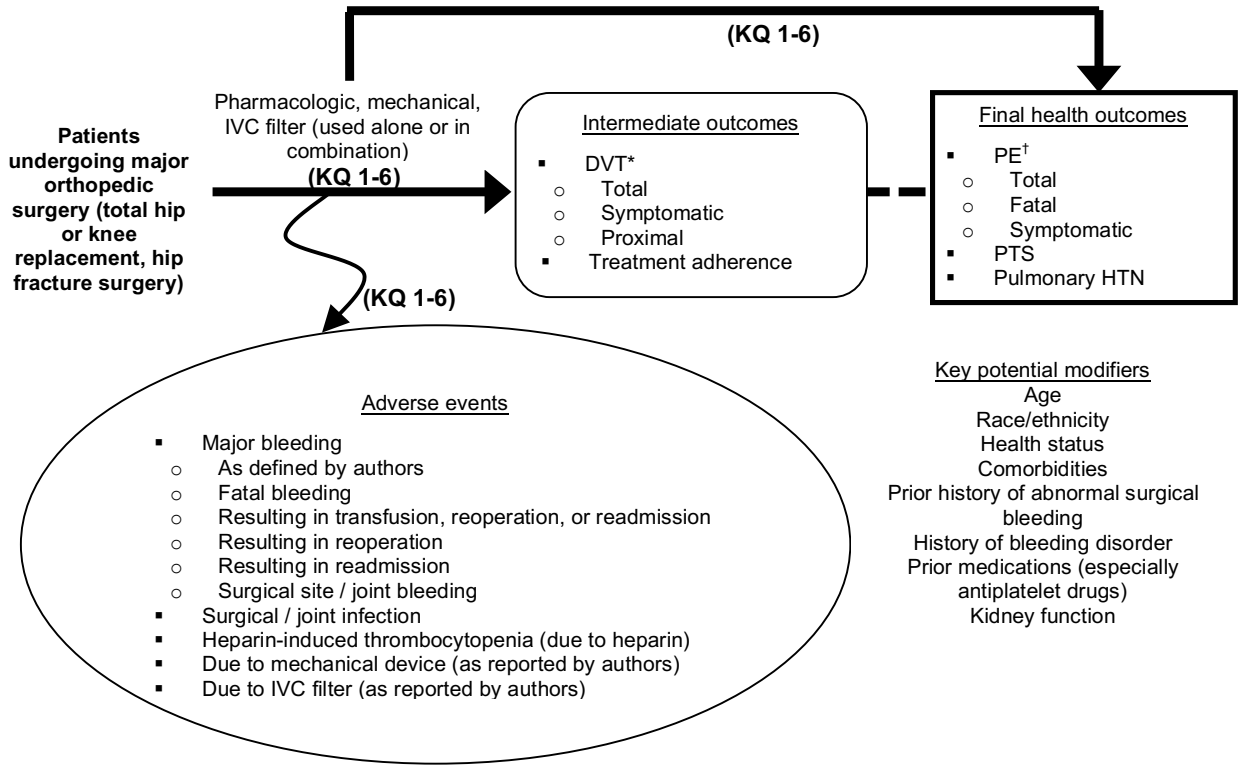
Setting

- In hospital (with or without continuation of intervention after discharge)

III. Analytic Framework

To guide the assessment of studies that examine the effect of thromboprophylaxis on final, intermediate, and adverse outcomes in patients undergoing major orthopedic surgery the analytic framework maps the specific linkages associating the populations of interest, the interventions, modifying factors, and outcomes of interest. The analytic framework depicts the chains of logic that evidence must support to link the studied interventions studied.

Figure 1. Analytic framework for the comparative effectiveness of venous thromboembolism prophylaxis in orthopedic surgery



DVT = deep vein thrombosis, HIT = heparin-induced thrombocytopenia, IVC = inferior vena cava, KQ = key question(s), PE = pulmonary embolism, PTS = postthrombotic syndrome, Pulmonary HTN = pulmonary hypertension, VTE = venous thromboembolism

* DVTs are the principal intermediate outcomes necessary for surgery-related PE or postthrombotic syndrome. Total DVTs (asymptomatic and symptomatic, or alternatively, proximal and distal) are of interest because, conceptually, all DVTs may result in PE or postthrombotic syndrome; although, symptomatic DVTs are believed to be a higher risk factor for postthrombotic syndrome and proximal DVTs are believed to be a higher risk factor for PE, particularly fatal PE. Asymptomatic and distal DVTs are not included in the list of DVTs of interest, since they are subsumed by total DVT and are not of great clinical interest alone. Of note, it would be equally reasonable to consider DVTs, especially symptomatic DVTs, to be final health outcomes.

† Total PEs includes both symptomatic and asymptomatic PEs, or alternatively, fatal and nonfatal PEs. Asymptomatic and nonfatal PEs are not included in the list of PEs of interest, since they are subsumed by total PE and are not of great clinical interest alone.

IV. Methods

The Evidence-based Practice Center (EPC) will conduct the review based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Comparative Effectiveness Reviews.[2]

Criteria for Inclusion/Exclusion of Studies in the Review – Please refer to Section II *The Key Questions*, where the Eligibility Criteria are listed after the KQs.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions: We will conduct literature searches of studies in PubMed, both the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, and EMBASE databases to identify primary research studies meeting our criteria. Searches will be limited to 2010 to current to overlap about 1 year with the search done for the 2012 AHRQ report. We will use the search strategies in Appendix A. The search strategy will be peer reviewed by an independent, experienced information specialist/librarian. We will ask the technical experts to provide citations of potentially relevant articles. We will search the ClinicalTrials.gov registry for completed relevant studies. We will peruse the reference lists of published clinical practice guidelines, relevant systematic reviews, and Scientific Information Packages from manufacturers. Any studies found from existing systematic reviews will be assessed and incorporated *de novo* from the original article. A major exception, is that we will use extracted and summarized data for studies from the 2012 AHRQ report. The Food and Drug Administration, Healthy Canadians, and the U.K. Medicines & Healthcare products Regulatory Agency websites were searched for potentially relevant studies during protocol development (the surveillance report); no additional studies were found. All articles identified through these sources will be screened for eligibility using the same criteria as was used for articles identified through literature searches. Peer and public review will provide an additional opportunity for experts in the field and others to ensure that no relevant publications have been missed. The search will be updated in all databases upon submission of the draft report for peer and public review. All summaries and qualitative and quantitative analyses in the update will incorporate all relevant studies, regardless of their source.

All citations (abstracts) found by literature searches and other sources will be independently screened by two researchers. At the start of abstract screening, we will implement a training session, in which all researchers will screen the same articles and conflicts will be discussed. During double-screening, we will resolve conflicts as a group. All screening will be done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). All potentially relevant studies will be rescreened in full text to ensure eligibility.

Data Extraction and Data Management: Each study will be extracted by one methodologist. The extraction will be reviewed and confirmed by at least one other experienced methodologist. Any disagreements will be resolved by discussion among the team. Data will be extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the Key Questions. Upon completion of the review, the SRDR database will be made accessible to the general public (with capacity to read, download, and comment on data). The basic elements and design of the extraction form will be the similar to those used for other AHRQ comparative effectiveness reviews and will include elements that address population characteristics; descriptions of the interventions, exposures, and comparators analyzed; outcome definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias questions.

Assessment of Methodological Risk of Bias of Individual Studies – We will assess the methodological quality of each study based on predefined criteria. For RCTs, we will use the Cochrane risk of bias tool,[3] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we will use relevant questions from the Newcastle Ottawa Scale.[4] Quality/risk of bias issues pertinent to specific outcomes within a study will be noted and considered when determining the overall strength of evidence for conclusions related to those outcomes.

Data Synthesis – All included studies will be summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. These included descriptions of the study design, sample size, interventions, followup duration, outcomes, results, and study quality.

We expect to conduct random effects model meta-analyses of comparative studies, if they are sufficiently similar in population, interventions, and outcomes. Specific methods and metrics (summary measures) to be meta-analyzed will depend on available, reported study data, but we expect to summarize odds ratios of the categorical outcome. Possible reasons for statistical heterogeneity will be explored qualitatively and, if appropriate data are available, we may also conduct metaregression analyses to evaluate study, patient, and intervention features and to evaluate dose-response. We will explore subgroup differences within (and possibly across) studies.

To address Key Question 5, we plan to conduct a network meta-analysis of RCTs for risk of DVT and of major bleeding (total) to compare all treatment alternatives across studies. The exact methodology to conduct the network meta-analysis has not yet been determined, but we will confer with international experts in network meta-analysis. We expect to conduct 12 analyses. For each of three surgeries (THR, TKR, and hip fracture surgery) and for two outcomes (total DVT and major bleeding), we will conduct two analyses: 1) comparisons of classes of thromboprophylaxis interventions (e.g., low molecular weight heparin, factor Xa inhibitors) and 2) comparisons of individual interventions. Ideally, we will treat different doses of interventions as separate interventions, but this will depend on the state of the evidence; studies of different doses may need to be lumped. We plan to include placebo-controlled trials derived from the 2012 Report and any 3- or more arm study with a placebo arm. The choice of outcomes to be evaluated by network meta-analysis was based on their importance to clinicians and patients when choosing among interventions and the likelihood of there being sufficient evidence. (We deemed it unlikely there would be sufficient evidence to analyze PE, since the outcome rarely occurs.) Full methodology for conducting the network meta-analyses will be reported, as will all results and assessments of model fit, coherence, and consistency.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: We will grade the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[5] We plan to assess the strength of evidence for each principal health outcome, as determined with input from the panel of technical experts: total VTE, symptomatic VTE, PE, DVT, and adverse events. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk

of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we will assign a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating will be summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating.

Assessing Applicability: We will assess the applicability within and across studies with reference to adults undergoing major orthopedic surgery. At a minimum, factors of interest to assess applicability will be the key potential modifiers listed in the Analytic Framework (e.g., age, race/ethnicity, health status).

V. References

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3. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928. PMID: 22008217.
4. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. . The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses: Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Last accessed 7/25/2015.
5. Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care: Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.

VI. Definition of Terms

Deep vein thrombosis (DVT): A blood clot in a deep vein (i.e., a vein that is not close to the body's surface).

> **Distal DVT**: A deep vein thrombosis below the knee in the calf veins. These clots are generally smaller and less likely to embolize to the lungs than proximal DVTs
>
> **Proximal DVT**: Thrombosis in a vein above the knee and below the vena cava, including in the popliteal, femoral, and iliac veins. These clots tend to be relatively large and may be more liable to embolize to the lungs, compared to clots in more distal veins.

Mechanical thromboprophylaxis: Mechanical devices for the prevention of venous thromboembolism. These mostly work by preventing pooling of blood in the lower extremities either by applying pressure to the lower extremities (and their veins) or by maintaining movement of the lower extremity, which helps to pump blood back toward the heart. Preventing blood pooling lowers the risk of blood clots forming.

Network MA: A meta-analysis in which multiple treatments are compared using both direct comparisons of interventions within randomized controlled trials and indirect comparisons across trials.

Pharmacologic thromboprophylaxis: Medical drug therapy for the prevention of venous thromboembolism. Available drugs are anticoagulants that lower the likelihood that blood clots.

Postthrombotic syndrome: Chronic swelling and pain resulting from a blood clot's damage to the veins and valves. This is thought to occur due to physical damage to the vein and valves and ongoing inflammation. It is associated with pain, swelling, discoloration, and ulceration.

Pulmonary embolism: Blockage of the pulmonary artery (the artery carrying deoxygenated blood from the heart to the lungs) or one of its branches by an embolism, such as a broken off clot that has traveled from elsewhere in the body through the bloodstream. The blockage can result in sudden cardiovascular collapse including hypoxemia (low oxygen level in the blood), hypotension (low blood pressure), arrhythmias, and death.

Regimen: In regards to this protocol, regimens refer to different ways that interventions are given or used, referring primarily to mechanical interventions. Examples include different frequencies, ranges of motion, or intensities of joint movement or venous compression.

Venous thromboembolism: Composite of two related conditions, deep vein thrombosis and pulmonary embolism

VII. Summary of Protocol Amendments

No protocol amendments.

VIII. Review of Key Questions

AHRQ posted the Key Questions on the Effective Health Care Web site for public comment. The EPC refined and finalized the Key Questions after review of the public comments, and further input from Technical Experts. This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants

Key Informants were not used to develop the protocol for the systematic review update.

X. Technical Experts

Technical Experts constitute a multidisciplinary 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 3 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 290 2012 00012 I 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

Literature Searches

PUBMED

"Arthroplasty, Replacement, Knee"[Mesh] or ("Arthroplasty"[Mesh] and (knee or hip)) or total knee replacement or knee arthroplasty or tkr or "Knee Prosthesis"[Mesh] or knee prosthesis or knee joint or "Arthroplasty, Replacement, Hip"[Mesh] or total hip replacement or hip arthroplasty or thr or "Hip Prosthesis"[Mesh] or Hip Prosthesis or hip fracture surgery or hfs or (("Fracture Fixation, Internal"[Mesh] or "Fracture Fixation, Intramedullary"[Mesh]) and (hip femur or femor* or tibia* or ankle or foot)) or (arthroscop* and (knee or meniscectomy or synovectomy or cruciate ligament)) or "Casts, Surgical"[Mesh] or surgical cast or plaster cast or splint* or "Splints"[Mesh] or Achilles tendon or tibial plateau fracture or distal femur fracture or (lumbar and (laminectomy or discectomy or fusion)) or (osteotomy AND (femur OR femor* OR tibia*))

AND

"Pulmonary Embolism"[Mesh] or pulmonary embol* or pulmonary thromboembol* or PE or deep vein thrombos* or deep venous thrombos* or deep venous thromboembol* or deep vein thromboembol* or DVT or "Venous Thromboembolism"[Mesh] or venous thromboembol* or VTE or "Venous Thrombosis"[Mesh] or venous thrombos* or clot

AND

"Anticoagulants"[Mesh] OR "Aspirin"[Mesh] or aspirin or clopidogrel or ticlopidine or prasugrel or "Heparin"[Mesh] or "Heparinoids"[Mesh] or heparin or UFH or LMWH or enoxaparin or dalteparin or nadroparin or ardeparin or bemiparin or certoparin or parnaparin or reviparin or tinzaparin or danaparoid or fondaparinux or idraparinux or rivaroxaban or apixaban or enoxaparin or "Hirudins"[Mesh] or desirudin or argatroban or bivalirudin or lepirudin or dabigatran or "Warfarin"[Mesh] or warfarin or "4-Hydroxycoumarins"[Mesh] or acenocoumarol or dicoumarol or "Dextran Sulfate"[Mesh] or dextran sulfate or "Stockings, Compression"[Mesh] or ((compression or elastic) and (stocking* or boot*)) or ~~GCS~~ or venous foot pump or VFP or "Intermittent Pneumatic Compression Devices"[Mesh] or pneumatic compression or pneumatic hose or pneumatic compression hose or IPC or "Vena Cava Filters"[Mesh] or vena cava filter* or IVC or "Factor Xa Inhibitors"[Mesh]

AND

"Cohort Studies"[Mesh] OR cohort OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR (follow-up or followup) OR longitudinal OR "Placebos"[Mesh] OR placebo* OR "Research Design"[Mesh] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Comparative Study"

[Publication Type] OR ((comparative or Intervention) AND study) OR "Intervention Studies"[Mesh] OR pretest* OR pre test* OR posttest* OR post test* OR prepost* OR pre post* OR "before and after" OR interrupted time* OR time serie* OR intervention* OR (("quasi-experiment*" OR quasiexperiment* OR quasi or experimental) and (method or study or trial or design*)) OR "Case-Control Studies"[Mesh] OR (case and control) OR "Clinical Studies" [Publication Type] OR "Clinical Studies as Topic"[Mesh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random* OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Placebos"[Mesh] OR placebo OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) OR rct

Limit 2010-2015

COCHRANE

(Arthroplasty and (knee or hip)) or total knee replacement or knee arthroplasty or tkr or "Knee Prosthesis"[Mesh] or knee prosthesis or knee joint or total hip replacement or hip arthroplasty or thr or Hip Prosthesis or hip fracture surgery or hfs or ((Fracture Fixation Internal or Fracture Fixation Intramedullary) and (hip femur or femor* or tibia* or ankle or foot)) or (arthroscop* and (knee or meniscectomy or synovectomy or cruciate ligament)) or surgical cast or plaster cast or splint* or Achilles tendon or tibial plateau fracture or distal femur fracture or (lumbar and (laminectomy or discectomy or fusion)) or (osteotomy AND (femur OR femor* OR tibia*))

AND

Pulmonary Embolism or pulmonary embol* or pulmonary thromboembol* or PE or deep vein thrombos* or deep venous thrombos* or deep venous thromboembol* or deep vein thromboembol* or DVT or Venous Thromboembolism or venous thromboembol* or VTE or Venous Thrombosis or venous thrombos* or clot

AND

Anticoagulants or Aspirin or clopidogrel or ticlopidine or prasugrel or Heparin or Heparinoids or UFH or LMWH or enoxaparin or dalteparin or nadroparin or ardeparin or bemiparin or certoparin or parnaparin or reviparin or tinzaparin or danaparoid or fondaparinux or idraparinux or rivaroxaban or apixaban or enoxaparin or Hirudins or desirudin or argatroban or bivalirudin or lepirudin or dabigatran or Warfarin or warfarin or 4-Hydroxycoumarins or acenocoumarol or dicoumarol or (dextran and sulfate) or ((compression or elastic) and (stocking* or boot*)) or venous foot pump or VFP or "Intermittent Pneumatic Compression Devices" or pneumatic compression or pneumatic hose or pneumatic compression hose or IPC or vena cava filter* or IVC or Factor Xa Inhibitors

Limit 2010-2015

EMBASE

(Arthroplasty and (knee or hip)) or total knee replacement or knee arthroplasty or tkr or knee prosthesis or knee joint or total hip replacement or hip arthroplasty or Hip Prosthesis or hip fracture surgery or (Fracture Fixation and (femur or femor*))

AND

Pulmonary Embolism or pulmonary embol* or pulmonary thromboembol* or deep vein thrombos* or deep venous thrombos* or deep venous thromboembol* or deep vein thromboembol* or DVT or Venous Thromboembolism or venous thromboembol* or VTE or Venous Thrombosis or venous thrombos* or clot

AND

Anticoagulants or Aspirin or clopidogrel or ticlopidine or prasugrel or Heparin or Heparinoids or UFH or LMWH or enoxaparin or dalteparin or nadroparin or ardeparin or bemiparin or certoparin or parnaparin or reviparin or tinzaparin or danaparoid or fondaparinux or idraparinux or rivaroxaban or apixaban or enoxaparin or Hirudins or desirudin or argatroban or bivalirudin or lepirudin or dabigatran or Warfarin or warfarin or 4-Hydroxycoumarins or acenocoumarol or dicoumarol or (dextran and sulfate) or ((compression or elastic) and (stocking* or boot*)) or venous foot pump or VFP or "Intermittent Pneumatic Compression Devices" or pneumatic compression or pneumatic hose or pneumatic compression hose or IPC or vena cava filter* or IVC or Factor Xa Inhibitors

AND

cohort OR (follow-up or followup) OR longitudinal OR placebo* OR ((comparative or Intervention) AND study) OR pretest* OR pre test* OR posttest* OR post test* OR prepost* OR pre post* OR (before and after) OR interrupted time* OR time serie* OR intervention* OR ((quasi-experiment* OR quasiexperiment* OR quasi or experimental) and (method or study or trial or design*)) OR (case and control) OR clinical stud* OR clinical trial OR random allocation OR double-blind method OR single-blind method OR random* OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) OR rct

Limit 2010-2015