Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Venous Thromboembolism Prophylaxis in Orthopedic Surgery*

Draft review available for public comment from May 25, 2011 to June 22, 2011.

Research Review Citation: Sobieraj DM, Coleman CI, Tongbram V, Lee S, Colby J, Chen WT, Makanji SS, Ashaye A, Kluger J, White CM. Venous Thromboembolism in Orthopedic Surgery. Comparative Effectiveness Review No. 49. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 12-EHC020-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

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

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

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	Abbreviations page needs to be completed.	The abbreviations which are used in the text of the report are found right before the references and can be easily located using the table of content. We greatly limited the use of abbreviations in the text. Abbreviations used in tables are defined in the legend under the given table.
Peer Reviewer #1	General	Page numbers need to be corrected throughout the report (for example, KQs 2 through 3 all show page 71).	Thank you for this comment. We have assured the page numbering follows the AHRQ publishing guide.
Peer Reviewer #1	General	Some instances of blank space; formatting can be improved.	Thank you, blank spaces have been removed.
Peer Reviewer #1	General	As provided, the title page only contains the title of the report, but no authors; also, the acknowledgments page does not contain the contact information for key informants or technical expert panel. Not sure if this due to a blinded review or an oversight.	Thank you for this comment. We are required to remove all mention of the EPC and individuals from the draft report, which is what was available for peer review. The final report will be complete with this information.
Peer Reviewer #1	General	Please ensure that vitamin K antagonists is appropriately capitalized in all instances. There are a few instances where the K appears as k.	Thank you for this comment. We have checked all instances to make sure “K” is appropriately capitalized.
Peer Reviewer #1	General	Consistency in language: In some instances, the subgroup analysis is labeled "2001-present" and in others, "2001 to the present". See comment below regarding changing label to be more specific than “present.”	Thank you for this comment. We have checked to make sure the use of “2001-present” is consistently used throughout the report and is now defined in the methods section so that in subsequent years the reader will be able to easily identify the timeframe.
Peer Reviewer #1	Executive Summary	In the methods section, please justify how the sample size of 750 was chosen for the observational studies. Can this be cited in a methods guide?	Thank you for this comment. This decision was made with the Technical Expert Panelist in the development of this protocol, which also was posted for comment. Observational studies that enrolled <750 subjects were excluded because numerous RCTs in this literature base enroll over 500 participants, with the most contemporary trials enrolling over 1,000 participants. Therefore observational studies would need to be of larger size to provide additional valuable information on outcomes of interest and applicability. This is stated in the main report, however clarification has been added to the executive summary.
Peer Reviewer #1	Executive Summary	When describing the rating of applicability, please clarify that this would be in an orthopedic surgery population, not a primary care/outpatient population.	Thank you for this comment. We have clarified in the executive summary and in the main report we are referring to the orthopedic surgery population.
Peer Reviewer #1	Executive Summary	In the report of results for KQ 1, there is a series of percents for THR, TKR, and HFS, respectively. In some cases, the value is shown as "--"; please define this symbol. My guess is that there is no data, but would be clearer if stated as "no data".	Thank you for this comment. In both the executive summary and the main report we have defined the symbol “--“ as suggested, which we have used in place of “no data available”.
Peer Reviewer #1	Executive Summary	KQ 8: First word should be either "prolonged" or "prolonging"	Thank you for this comment. We have changed the first word to state “prolonged”.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Executive Summary	Discussion: Page ES-18, Line 41, Sentence stating "UFH should not be an initial prophylactic strategy" sounds too much like a recommendation and not a presentation of solely the evidence. Please rephrase.	Thank you for this comment. We have removed any statement from the report which implies a recommendation.
Peer Reviewer #1	Abstract	As above, please define symbol "--".	See comment above from Peer Reviewer #1, executive summary.
Peer Reviewer #1	Table of content	In the Table of Tables, there are some entries with an asterisk at the end of the title. Please define or remove the asterisk.	Thank you for this comment. We have removed the asterisk from the table of tables.
Peer Reviewer #1	Methods	Please justify how the sample size of 750 was chosen for the observational studies. Can this be cited in a methods guide?	See comment above from Peer Reviewer #1, executive summary.
Peer Reviewer #1	Methods	Page 8 (and others): FDA should be spelled out as "Food and Drug Administration" not "Federal Drug Administration".	Thank you for this comment. All instances referring to the FDA now state “Food and Drug Administration”.
Peer Reviewer #1	Methods	Clarify if the outcome of "mortality" is "all-cause mortality".	Thank you for this comment. In the analytic framework, we define mortality as “all cause mortality” in the legend.
Peer Reviewer #1	Methods	Justify the appropriateness of exclusion of trials and trial arms in pooled analyses due to no events. The report of a zero event rate is valuable information related to the baseline risk of events. By excluding this important data, there is a risk that the pooled results as given may overestimate the effect of the intervention, being more likely to show statistically significant differences between interventions, when there may truly be none.	Thank you for this comment. The standard practice in meta-analysis of odds ratios and risk ratios is to exclude studies from the meta-analysis where there are no events in both arms. This is because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect. So that the reader is able to easily determine which studies had no events for each analysis, the studies were included in the forest plot and instead of a RR or OR the statement “excluded” appears, since an effect cannot be calculated. When studies are excluded because of no events, we explicitly state this in the text as well. (See Methods Guide for Comparative Effectiveness Reviews available at: http://effectivehealthcare.ahrq.gov/ehc/products/243/554/MethodsGuide--ConductingQuantitativeSynthesis.pdf)

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Methods	Justify the appropriateness of the method used to calculate NNT and NNH. It is unclear as written which numbers were used to calculate. Please clarify. One method may be to utilize the control event rate in an equation and calculate NNT and NNH from the upper and lower limits of the pooled 95% confidence interval. It is unclear if this was completed from the text as written. If this was the case, please provide the applicable estimation equations. Also, please explain why NNT and NNH were not calculated from pooled absolute risk differences, which would provide a more accurate value than an estimation from relative risks. Related to the comment above regarding the exclusion of trials with zero events, the NNT and NNH would be biased estimates of the absolute differences between interventions. By excluding this very important zero event data, it is likely that the NNT and NNH would be underestimated in the report results.	Thank you for the comment. The methods for calculating NNT and NNH were clarified in the methods section of the text. Calculating a NNT or NNH using the pooled absolute risk difference assumes a fixed control event rate and may be misleading if the population the result is applied to has a varying levels of baseline risk for the outcome. A patient with a lower baseline risk will have a higher NNT and vice-a-versa. Therefore, to account for the variability in baseline risk that may be seen in clinical practice, the range of control event rates in the individual trials for a pooled analysis were considered when calculating the NNT and NNH. An equation which utilizes the control event rate and the relative effect estimate was applied to the lowest and highest control event rate in the range and then the NNT and NNH were reported as a range. This will allow clinicians to see the range based on variable baseline risk. When a trial with no events was included in the pooled analysis, a range could not be calculated for the NNT or NNH and this was explicitly stated in the text.
Peer Reviewer #1	Methods	Subgroup analyses: From the included data extraction form, it is not clear if subgroup analyses from individual included trials was extracted and then analyzed for the subgroups of age, gender, and ethnicity. By extracting this information, there may be more evidence regarding subgroups than otherwise presented in this report. If an individual trial did not conduct any subgroup analyses upon the relevant variables, it would also be useful to know, so that we can inform future researchers to conduct such subgroup analyses. It appears that this was done in the results section, but this should be made explicit in the methods section.	Thank you for this comment. We did look for specific information in each trial by age, gender, and ethnicity. A sentence was added to the methods, data extraction section, to clearly state this type of information was sought. In Appendix B, we present the data extraction form used. At the end of the form a question is asked “Does This trial or study have sub group analysis looking at age, gender and ethnicity?” If the individual extracting data answers “yes”, they are prompted to report the subgroup analysis results.
Peer Reviewer #1	Methods	Suggest rewording the subgroup for "2001 to present" to "2001 to 2011" so that the end date will be explicit for future readers.	See comment above from Peer Reviewer #1, general.
Peer Reviewer #1	Methods	When describing the rating of applicability, please clarify that this would be in an orthopedic surgery population, not a primary care/outpatient population.	See comment above from Peer Reviewer #1, executive summary.
Peer Reviewer #1	Results	Literature Search 1.The position of Table 4 seems irrelevant to this section, as it describes the summary of results to key questions and not a result of the literature search.	Thank you for this comment. In the past we have had comments to include a comprehensive results table in the beginning of reports rather than the last table that appears in the report. For this reason we have chosen to place a summary table prior to the presenting of results per key question.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	KQ 2 2.The key points of this section state quite boldly that there is "no impact" of various surgical and patient characteristics on the risk of outcomes. However, given the lack of statistical significance and low strength of evidence from these evaluations, this seems to be an overstatement of the evidence.	Thank you for this comment. The key points for KQ 2 were revised so that is clear as to which characteristics had strength of evidence of high, moderate, or low, and now clearly defines those which the data were insufficient.
Peer Reviewer #1	Results	3.Study design and characteristics: When only a selection of included studies report a specific baseline characteristic (e.g. mean weight, and primary surgery), please provide references for those studies.	Thank you for this comment. Referencing has been added as suggested.
Peer Reviewer #1	Results	KQ 3 1.The key point stating that the "available clinical trials were not very informative" sounds too much like commentary, rather than a statement of the low strength of evidence.	Thank you for this comment. The language was modified to state that “The available clinical trials provided insufficient data….” Instead of “were not very informative”.
Peer Reviewer #1	Results	2.Study design and characteristics: When only a selection of included studies report a specific baseline characteristic, please provide references for those studies.	Thank you for this comment. Referencing has been added as suggested.
Peer Reviewer #1	Results	KQ 4 1.When subgroup analyses were not possible because there was only a single relevant trial, please state which subgroups this individual trial would have applied to and report results as such.	Thank you for this comment. When subgroup analyses were not possible because there was a single relevant trial, we have provided the details about the individual study (i.e which surgery, what the intervention was, if the trial was considered “true placebo” etc.) so that the reader can judge which subgroup the study would have applied to, in order to minimize repetition of information.
Peer Reviewer #1	Results	2.Improve consistency in language; in some instances, statistical heterogeneity and publication bias could not be assessed because of "too few studies" and in other instances "too few strata".	Thank you for this comment. All instances now consistently state “too few studies”.
Peer Reviewer #1	Results	3.For the outcome of readmission, please provide information about the cause of readmission.	Thank you for this comment. The reasons for readmission that were provided in the text of the study are now reported in the results section of KQ 4.
Peer Reviewer #1	Results	4.Table 10: Recommend adding symbol for those results which are statistically significant.	Thank you for this comment. A symbol has been inserted to designate statistically significant results.
Peer Reviewer #1	Results	KQ 5 1.It is quite obvious that KQ4 and KQ5 were written by two different individuals. Consider unifying the language used.	Thank you for this comment. We have applied consistent rules across all key questions in order to provide unity, although the questions differ from each other enough so that the writing may reflect the needs of that particular key question.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	In some cases where the analysis found high degrees of heterogeneity, this is explained by commenting on the direction and magnitude of effect, but this is not consistent through all outcomes which showed high heterogeneity. Please be consistent in providing this explanation.	Thank you for this comment. We have gone through and more consistently provided the explanation of high heterogeneity.
Peer Reviewer #1	Results	3. Please provide a statement of either the absence of controlled observational studies or the results of existing controlled observational studies for all outcomes reported in KQ5.	While we appreciate the comment, our format for handling observational data in each KQ was to report presence of observational data and results when available. The one exception was when no data whatsoever (RCT or observational) was available, in that instance it was stated so.
Peer Reviewer #1	Results	4.The Methods section states that studies published prior to 2001 is an analyzed subgroup, but these results are not presented.	Thank you for this comment. When subgroup analysis based on trials published from 2001-present was possible (2 or more trials) we provided the results. The results of this subgroup analysis can also be found in the summary table following the KQ5 results text.
Peer Reviewer #1	Results	5.When subgroup analyses were not possible because there was only a single relevant trial, please classify which subgroups this individual trial would have applied to and report results as such.	Please see response above, Peer Reviewer #1, KQ 4 results.
Peer Reviewer #1	Results	6.Page 120, distal DVT outcome, LMWH vs DTI outcome, "included two separate comparisons" is mentioned twice for the trial by Ginsburg et al.	Thank you for this comment. The duplicate wording has been removed.
Peer Reviewer #1	Results	7.For the outcomes of discomfort and readmission, please provide descriptions of definitions per study. Not sure if this is in the Appendix Tables, as this is not referenced within the body of the text.	Thank you for this comment. The reasons for readmission and the definitions of discomfort were added to the text.
Peer Reviewer #1	Results	8.Table 11 title has the word "question" misspelled.	Thank you for this comment. The spelling of the title for Table 11 has been corrected.
Peer Reviewer #1	Results	9.Consistency in abbreviations: Factor Xa inhibitors have been abbreviated as FXA and as FXI in various sections of the report.	Thank you for this comment. The terminology “factor Xa inhibitor” and its abbreviations are now consistently used throughout the report and executive summary.
Peer Reviewer #1	Results	10.Table 12: Recommend adding symbol for those results which are statistically significant.	Thank you for the comment. A symbol has been added to show statistically significant results.
Peer Reviewer #1	Results	11.Table 12 and 10 have different formats in presentation of subgroup results. Please unify.	While we appreciate the comment, we have organized each of these tables to fit the needs of the individual key questions. In key question 4 the base case analysis is pharmacologic prophylaxis versus no prophylaxis or mechanical prophylaxis versus no prophylaxis. Key question 5 has many more base case analyses since each comparison between two different pharmacologic or mechanical classes is represented.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	12.Table 12: Define symbol "---"	Thank you for your comment. The symbol "---" has been defined in the table legend and in the text where it appears in key question 1.
Peer Reviewer #1	Results	KQ 6 1.For this KQ, it is not clear from the methods that all enoxaparin trials would be pooled together to generate an "other" arm. Please specify that this was done in the methods sections.	Thank you for this comment. The methods now state that for key question 6, data will be pooled for like agents versus others in the class when possible.
Peer Reviewer #1	Results	2.Comment on the inability to perform subgroup analyses for specific comparisons, when applicable, similar to the way this was reported in KQs 4 and 5.	Please see response above, Peer Reviewer #1, results, KQ4
Peer Reviewer #1	Results	3.Comment on the lack of controlled observational studies, as applicable.	Please see response above, Peer Reviewer #1, results, KQ4
Peer Reviewer #1	Results	KQ 7 1.Recommend adding subheadings for "pharmacological plus mechanical versus pharmacological alone" and for "pharmacological plus mechanical versus mechanical alone" to improve ease of reading for each outcome.	Thank you for this comment. Where possible the suggested subheadings were used in key question 7.
Peer Reviewer #1	Results	2.There is inconsistent reporting of specific interventions in individual trials. Some outcomes specifically report which interventions were evaluated, but others do not. Would prefer to see which interventions were included in each outcome, regardless of the occurrence of any outcome events. This would be important to the reader in interpreting potential heterogeneity or other factors which may influence the lack of events.	Thank you for this comment. The interventions being compared are listed in all cases, even when no events occurred in any of the trials which reported the given outcome.
Peer Reviewer #1	Results	3.Also, should report study characteristics such as type of surgery or other factors related to subgroups, even if no events occurred.	Thank you for this comment. To balance the text of the report with available tables in the appendix, when trials reported no events, they are cited and the trial characteristics (including any information which may be needed to determine applicability of a particular subgroup) can be found in the appendix tables.
Peer Reviewer #1	Results	4.For the mortality section, please cite individual trials when reporting their individual results.	Thank you for this comment. The individual trials are now cited in this section.
Peer Reviewer #1	Results	5.Table 14: As before, define symbol "---"	Thank you for this comment, a definition of the symbol "---" has been added to the legend.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	KQ 8 1.Soften the language stating that any particular intervention "reduces" or "increases" events, especially considering the low strength of evidence.	Thank you for this comment. For summary tables, we use a conclusion which shows directionality and then provide the strength of evidence. In CER, one needs to appreciate not just the direction and magnitude but also the strength of evidence and the applicability of that evidence when making healthcare decisions. One should not be viewed in a vacuum. Therefore we feel the language used accurately describes the statistical significance of the result taking into consideration the strength of the evidence
Peer Reviewer #1	Results	2.For all studies included in the analysis, it is valuable to know which specific interventions are being evaluated. Provide this information either in text or reference the applicable table. Knowing the specific intervention would be more insightful than simply knowing the duration of therapy because some interventions may be more effective in prolonged durations while others may not.	Thank you for this comment. The introduction to this key question specifies what the intervention was for each trial included in the key question. Alternatively, the reader can refer to the tables in the appendix which display the trial characteristics to find this information.
Peer Reviewer #1	Results	3.It is already stated in the study design and characteristics section that no controlled observational trials are included in this KQ. There is no need to repeat this information again within individual outcomes for which there is no data.	Thank you for this comment. Although the introduction does state this fact, our standard procedure for all key questions when no data was available (RCT or observational) was to state so.
Peer Reviewer #1	Results	1.Provide relative risks and confidence intervals for studies included. If not available in the publication, please state such.	Thank you for this comment. Calculation of relative risk and odds ratio, whether pooled or not, was conducted using the raw numerical data extracted from traisl (number of events and total number of subjects, per group). The individual study relative risk or odds ratio (depending on the pooled effect) along with its confidence interval, can be found in the respective forest plot for the particular outcome. When only one trial was available we report the calculated relative risk or odds ratio with the confidence interval in the text.
Peer Reviewer #1	Appendix	Appendixes 1.The table of contents appears as underlined hyperlinks. This is difficult to read in print; please remove style.	Thank you for this comment, the formatting has been addressed.
Peer Reviewer #1	Appendix	2.Tables: Please repeat Table Title on every page, for ease of reading	Thank you for this comment. The publishing guide for comparative effectiveness reports specifies to repeat header rows rather than breaking tables to insert the table title on every page of the table.
Peer Reviewer #1	Appendix	3.The Egger's p-value is given for some forest plot figures, but not all. Please add missing Egger's p-values throughout the appendix.	Thank you for this comment. The Egger's p-value was only provided for what was considered to be a base case analysis, since restricting the studies in a particular analysis, such as the subgroup analyses, inherently creates publication bias.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Appendix	4.It seems that the analysis presented in Figure 53, on the impact of pharmacologic prophylaxis versus none on minor bleeding (2001-present) should be a relative risk, rather than a Peto odds ratio, since Peto odds ratio is reserved for rare events. Verify that this is the correct analysis, based on the pre-specified criteria for choosing Peto odds ratio over relative risk.	Thank you for this comment. This outcome was updated to account for new literature which reported applicable data, and the new analysis was run as a relative risk, which followed the pre-specified criteria set in the methods.
Peer Reviewer #1	Appendix	5.Figure 105, LMWH versus DTI on mortality (2001-present): Studies were excluded in this analysis, even though it reports a random effects relative risk. The Cochrane Handbook states that zero-cell adjustments are not necessary for Peto odds ratio; however, adjustments should be made with relative risk. – same comment applies for Figure 152 , 153, 159, 219	Thank you for this comment. The protocol followed for this report was a collaborative effort on behalf of the EPC and the members of the Technical Expert Panel. The methodology of the report states that trial in which no event occurred were excluded from the pooled analysis. The standard practice in meta-analysis of odds ratios and risk ratios is to exclude studies from the meta-analysis where there are no events in both arms. This is because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect. While it may be clear that events are very rare on both the experimental intervention and the control intervention, no information is provided as to which group is likely to have the higher risk, or on whether the risks are of the same or different orders of magnitude (when risks are very low, they are compatible with very large or very small ratio measures). Zero cell correction meets the objective of avoiding computational errors although it usually has the undesirable effect of biasing study estimates towards no difference and overestimating variances of study estimates (consequently down-weighting inappropriately their contribution to the meta-analysis). (See Cochrane Handbook for Systematic Reviews)
Peer Reviewer #1	Discussion and Conclusion	no comments	NA
Peer Reviewer #1	Clarity and Usability	no comments	NA
Peer Reviewer #2	General	The information in this massive, well executed undertaking accurately describes the current state of the art regarding prophylaxis for thromboembolic disease. However, I have major reservations with the conclusions derived from this information. After reading this text, it appears to me that the major conclusions should be; --at this time, there is not enough high level, consistent, complete data, to make any firm conclusions about the management of this problem. My reasoning is noted below.	Thank you for this comment. We hope to have addressed the reservations you have below while addressing the specific comments made.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Abstract	First, I must comment on the Abstract. This undoubtedly will be the most read 943 words of this entire 970 page manuscript. The Conclusions in the Abstract and the information the authors have elected to include in the Results may be misleading, possibly inaccurate, and almost appear to have been written by a representative of the pharmaceutical industry. For example in Conclusions they state: "the incidence of DVT is appreciable but the risks of PE, major and minor bleeds is smaller". This statement is written despite the fact the authors determined that DVT may not be a surrogate marker for PE (they write "o While we found that there is a real risk of developing deep vein thrombosis, pulmonary embolism, and major bleeding after undergoing major orthopedic surgery, there is inadequate data to say whether or not deep vein thrombosis causes pulmonary embolism. We were not even able to determine that deep vein thrombosis is an independent predictor of pulmonary embolism). Therefore, it seems inconsistent to make a comment about the incidence of DVT being 'appreciable', when DVT have no known significance, and in the same sentence make an association to the risk of PE. It would seem more accurate to state: --DVT are relatively common but we are unable to demonstrate they predict or cause PE. The risks of PE, major, and minor bleeds is small--.(may elect to define common and small).	Thank you for this comment. We have revised the conclusion as suggested, which now reads " In major orthopedic surgery, while the risk of developing deep vein thrombosis is highest followed by pulmonary embolism and major bleeding, there is inadequate data to say whether or not deep vein thrombosis causes pulmonary embolism or is an independent predictor of pulmonary embolism."
Peer Reviewer #2	Abstract	The Abstract Conclusion further states: "the benefit to harms is favorable for providing prophylaxis…." This conclusion is provided without defining benefits or harms. It appears the major benefit is reduced DVT, which they have demonstrated have undetermined or no significance, and the major harm is bleeding, which they have demonstrated (with high strength of evidence) to be significantly increased with prophylaxis. Further, they note in their Future Research section, the effects of increased bleeding on other outcomes needs to be evaluated. Therefore, I am unable to determine why this statement is a major conclusion as it is undefined, not investigated, and inconsistent with their observations.	Thank you for this comment. Overall benefits are those considered to be intermediate and final health outcomes while the harms include all adverse events due to therapy, which are all defined within the analytic framework provided within the report. There is insufficient evidence to say whether or not DVT causes PE or predicts PE. Therefore, the current state of the literature suggests that the overall benefits outweigh the overall harms in providing VTE prophylaxis in major orthopedic surgery. There are however, several pre-specified harms in which data was rarely reported and therefore in the future research avenues we have identified those harms which may add value in determining the overall benefit to harms (…"bleeding leading to infection, bleeding leading to transfusion, readmission and reoperation to provide more information for the comparative balance of benefits to harms.")

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Abstract	The Results section of the Abstract is equally perplexing. First, the inclusion of the statistical information makes this section difficult to read, is confusing and obfuscating. (However, that may be a format requirement). Second, it is not clear how the authors chose the information to be included in this paragraph. Some of the information is misleading and possibly inaccurate. For example, they state: In major orthopedic surgery, pharmacologic prophylaxis reduced major venous thromboembolism (VTE) [OR 0.21 (0.05-0.95), NNT 19-22, SOE: L, AOE: L], DVT [RR 0.55 (0.45-0.67), NNT 3-11,SOE: M, AOE: L], and proximal DVT (pDVT) [RR 0.53 (0.39-0.73,), NNT 6-79, SOE: M, AOE: L] but increased minor bleeding [RR 1.61 (1.12-2.32), NNH 4-166, SOE: H, AOE: M]. The focus is on reduced major VTE, despite the fact that buried within the details is the data noting the low strength of evidence (SOE). Also, the first sentence of Results notes the incidence of DVT and PE, but neglects to note that this may be historic data, over a 30 year period of time, and may not represent current practice (see below). It is unclear how they choose these statements, with low SOE, to be the first bits of information relayed in the Results. Are they the most important? How did the authors determine which information should be placed into the Abstract, (the most well read section of this text). Would it be more accurate and useful if the abstract reported the data which has high and low strengths of evidence, focusing the readers on what we really know and the current state of knowledge? Therefore, as written, I have strong reservations about the information, focus, and format of the Abstract as written.	Thank you for this comment. The abstract is structured as such so that it may stand alone and therefore statistical data is necessary. We had very little space for the abstract and this CER includes a large number of key questions with multiple comparisons. We applied a consistent format to all of the results reported in the abstract. The statistically significant findings for key questions were reported, and the strength of evidence was added to allow full and transparent interpretation of the results.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Result	Although the information in the text is excellent; the authors should address at least three systemic problems in their analysis. First, there is a selection bias. The authors find 3,464 cited articles and rely on 173 selected papers (120 RCT, 14 observational and 39 reviews). The majority of the RCT are industry supported studies (Appendix D) and designed to be drug comparison studies (that is why KQ 5 has so much data- 44 RCT). These excellent studies seek to determine if one drug agent is better than another and use DVT as a bioassay. As such, they exclude the elderly, frail, noncompliant patients, and compressive devices. The outcomes are DVT (95% are distal) and bleeding. This information has only modest clinical usefulness, yet because of the numbers and quality, has high SOE, may bias results. A corollary to this observation is the lack of data available to answer the other key questions. Since the bulk of the selected "good science" literature is drug company related, the other key questions remain incompletely answered because of the lack of data (0-3 RCT).	Thank you for this comment. The protocol followed for this report (including the literature search strategy and the inclusion/exclusion criteria) was a collaborative effort on behalf of the EPC and the members of the Technical Expert Panel. The literature search strategy was designed to balance sensitivity and specificity. The inclusion and exclusion criteria were strictly followed and review was completed in duplicate with disagreements resolved through discussion, a standard procedure for completion of systematic review. The PRISMA figure corresponding to key questions 1-9 demonstrates that the most common reason for exclusion was that the citation was not a systematic review, study, or trial (49%) followed by studies or trials which were not comparing interventions of interest to the a priori defined key questions (20%) and studies and trials outside of major orthopedic surgery (15%). Aside from being able to identify the funding source of the individual studies, little detail is ever provided as to the conflicts of interest that may or may not be present, and therefore one is left to assume the impact finding source may have on the trial. The applicability of the evidence is evaluated for every outcome and comparison made in base case analyses. The applicability of each individual trial can be found the appendix as well as the overall applicability rating to the body of evidence for each comparison and outcome evaluated in this report. Here the factors such as elderly, frail, inclusion of a representative population etc. are factored in. For this reason, although the strength of evidence may be moderate or high for some outcomes, the applicability of the body of evidence most times is low. (See the summary table in the executive summary, also in the beginning of the full report)

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Result	Second, is the selection of articles over a broad period of time. We cannot reliably use data from 20-30 years ago (published in the 80s and 90s) since the patterns of care have changed dramatically. Historically, total joint patients were kept in bed for prolonged periods of time, discharged at 2+ weeks, and maintained on restricted activity. Currently (past 10-15 yrs) patients are out of bed within 24 hrs and discharged within 2-4 days. It is believed this has significantly changed the incidence of TED. The data in KQ1 may have to be qualified as 12 of 18 citations are prior to 2000 and 6 of 18 prior to 1990.	Thank you for this comment. The Technical Expert Panel recognized the changes in practice and patient care over the years. However, there was agreement that excluding literature published earlier within the interval of 1980-present would most likely exclude placebo or control trials and limit further the literature base for those key questions. In order to evaluate the impact of practice and patient care changes, the experts agreed that a subgroup analysis for trials published from 2001 to the present would more accurately reflect contemporary practice, therefore this was the methodology used. We have added a comment to the key points to reflect the wide range of years in which studies were published and that the majority of trials were prior to 2000.
Peer Reviewer #2	Result	Third, the harvested data is essentially limited to VTE and bleeding (variably determined). These may not be the most important outcomes of interest to the patient and orthopaedic surgeons as they may be equally concerned about infection, range of motion, wound healing, chronic pain, etc. The need for this information is mentioned in “Future Research” but the current lack of information diminishes the conclusions that can be drawn from the available data.	Thank you for this comment. The selection of outcomes of interest (benefits and harms) is done so that the interests of a wide variety of stakeholders are considered. The outcomes which were defined in the report are a collaborative effort amongst the Technical Expert Panel members and the EPC and data was sought for each of these outcomes. Through the systematic review process it was determined that the current literature does not report or very rarely reports some of the pre-specified outcomes and mostly this impacted the harms. Therefore, we have identified this in the “limitations of current research” and “future research needs” since these outcomes may be of importance to individuals.
Peer Reviewer #2	Clarity and Usability	In summary, the data clearly demonstrates the state of the science. However, the weaknesses in the data should be clearly exposed, the conclusions clearly qualified, and the abstract rewritten.	Thank you for this comment. We have been able to address the specific comments made above in your review and therefore hope the overall clarity and usability has improved.
Peer Reviewer #3	General	1. The report is clinically meaningful although the data from newer agents recently published is not included.	Thank you for this comment. One of the inclusion criteria required for CER is that the drugs have a current FDA approved indication. The indication does not have to be for that which is under investigation. At the time of the initial literature search and the updated literature search in May 2011, rivaroxaban was not FDA approved for an indication, however given its recent approval (July 2011) an addendum to the CER has been added to discuss relevant clinical trials as they pertain to this CER. Apixaban has yet to be FDA approved for an indication and therefore is excluded from this CER.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	2. I have difficulty understanding the purpose of Key Question 3. Trials of DVT screened asymptomatic patients. VTE trials do not screen asymptomatic patients for PE. So if the only "meaningful" outcome to be considered is PE, then only contemporary trials which report the symptomatic VTE events, both DVT and PE, should be included. It appears that the purpose of this question is to identify some correlation between asymptomatic DVT and symptomatic PE.	Thank you for this comment. The purpose of this question is to identify literature which reviews the causal link between DVT and PE and reviews whether or not DVT can be accurately used as a surrogate marker for PE.
Peer Reviewer #3	General	3. The answer, based upon trials, to Key question #8 is different depending on whether or not the patient is undergoing TKR or THR. I am unclear why they are grouped together.	Thank you for this comment. As we are aware that the data may be different based on the individual surgery, we conducted subgroup analyses in each key question based on each of the three major surgeries and presented the results for these subgroups.
Peer Reviewer #3	Introduction	Please comment on the symptomatic versus asymptomatic DVT events reported in trials.	Thank you for this comment. We have added information, as suggested, to the introduction.
Peer Reviewer #3	Methods	1. Agree with inclusion criteria of using confirmed diagnosis for events.	Thank you for this comment.
Peer Reviewer #3	Methods	2. Agree with inclusion of observational trials since older data important to evaluate for questions 3 and 4.	Thank you for this comment.
Peer Reviewer #3	Methods	3. Search strategies and assessment of data quality adequately described.	Thank you for this comment.
Peer Reviewer #3	Methods	4. Table 2 page 53. Since there are no high SOE data, I would like to better know how the investigators synthesized the 4 EPC domains to make this grade recommendation.	Thank you for this comment. After the revision of the report based on all reviews, there are some outcomes which are now rated with a high strength of evidence. The four EPC domains of risk of bias, consistency, directness, and precision were used to rate strength of evidence, according to our described methods. Only RCT data was considered when grading the strength of evidence, and rating began as high and was downgraded accordingly based on the four domains. For further details as to what was considered in each domain, please refer to the methods paper published: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. J Clin Epidemiol 2010;63:513-23.
Peer Reviewer #3	Results	1. The amount of data presented in the literature search section is adequate.	Thank you for this comment.
Peer Reviewer #3	Results	2. If possible, can reference numbers accompany the studies identified in Table 4?	Thank you for this comment. This table presents only data which is rated with a strength of evidence rating of high, moderate, or low. Insufficient data is not presented. Additionally, the organization of the table is per key questions. Therefore, the interested reader can easily refer to the results chapter of the report to identify the included trials for outcomes and comparisons of interest.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	3. Table 4 (and elsewhere). I would recommend NOT using FXI as the abbreviation for Factor Xa inhbitors are there are indeed Factor XI inhibitors under investigation. Perhaps FXaI.	Thank you for this suggestion. We have changed “FXI” to FXaI” as suggested.
Peer Reviewer #3	Results	4. Table 4. Is KQ3 missing?	Thank you for this comment. As is noted by the * after the title of table 4, base case analyses with at least 1 randomized controlled trial or 1 controlled observational study and a strength of evidence of low, moderate, or high evaluating the given outcome are represented in this table. Since key question 3 was rated with an insufficient strength of evidence, it is not in Table 4.
Peer Reviewer #3	Results	5. Can Tables 7, 12, 13,14 and 15 have the Key question number somewhere in their title?	Thank you for this comment. We have added the key question to the title of these tables, as suggested.
Peer Reviewer #3	Results	6. The subheadings within each question answer make the responses easy to follow.	Thank you for this comment.
Peer Reviewer #3	Results	7. Can there be some discussion about major clinical trials that were omitted because they failed to have objective confirmation of events? For example No DTI studies.	Thank you for this comment. However, we are unsure of the meaning since direct thrombin inhibitors are included in this report. If the question is regarding factor Xa inhibitors, please see the reply above to your first comment under “general”.
Peer Reviewer #3	Results	8. Again for the DTIs and oral Xa inhibitors, please specify the search dates at every opportunity because this will be out-of-date before publication. For example on page 140 (86), the original analysis was limited to trials published since 2001 but it is still missing current trials published recently.	Thank you for this comment. This topic was also brought up by a second peer reviewier. We have explicitly stated the search inclusion dates in the methods and have clarified that 2001 to the present present is defined as 2001 through May 2011. Again, the inclusion of individual drugs is in part based on FDA approval. If an agent is not FDA approved at the time of the literature search or updated literature search, the drug is not included in the CER. Given rivaroxaban’s very recent approval (July 2011) we have added an addendum to the report reviewing pertinent clinical trial data.
Peer Reviewer #3	Results	9. Why wasn't the data with the DTI ximelagatran included? Please state in background.	Thank you for this comment. The inclusion of individual drugs is in part based on current FDA approval. Since ximelagatran, in the past, was once FDA approve but has since been removed from the US market, therefore no longer available for clinical use, the drug did not meet inclusion criteria. All agents evaluated in the CER must have a current FDA approved indication for use.
Peer Reviewer #3	Results	10. What were the search dates? Please add to Appendix 1 and text.	Thank you for this comment. The original search was conducted in July 2010 and the updated literature search was conducted in May 2011. This has been clarified in out methods section under the literature search as well as in Appendix A.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	11. Key Question 8, pages 252-253 (198-199). Why wasn't the subgroup of TKR analyzed? If it is negative, please be more clear in the conclusions. If there is insufficient data then state that (but I believe there are meta-analyses on just that so think there is sufficient data).	Thank you for this comment. However, we are unclear since TKR was evaluated as a subgroup and the results are presented within the key question. Since the results for TKR subgroup are based on a single comparison that was made within an RCT that included a second population (although evaluated separately) and because none of the outcomes were impacted to a statistically significant degree, specific comments were not made in the key points of this key question. However, given this suggestion, we have added a single statement to the key points to clarify this detail.
Peer Reviewer #3	Discussion/ Conclusion	1. The conclusions regarding Question 6 should be reviewed. If there are only 2 trials, then I do not think the authors should be a strong in their conclusion statements described on page 283 (229). Stating no differences when there are only two randomized trials is not clinically sound in my opinion.	Thank you for this comment. We agree that the literature base was insufficient for the majority of the outcomes evaluated. In a CER, aside from making a conclusion statement, the strength of the evidence is rated and must be taken into consideration when interpreting the conclusions. The strength of evidence was rated as insufficient for the majority of outcomes in this key question (Please see appendix Table 84). The key points for key question 6 also explicitly state the number of trials so that the reader is aware that the findings presented are based on a small literature base.
Peer Reviewer #3	Clarity and Usability	1. The structure is easy to follow with the exceptions identified above.	Thank you for this comment.
Peer Reviewer #3	Clarity and Usability	2. Overall I concur with the conclusions and most could be used to make practice decisions with three exceptions: 1) the work will be out-of-date with regarding to DTIs and Xa inhibitors. 2) I am concerned regarding Question 6, within class comparisons. Many would interpret only the statement in the summary/discussion to mean that all agents are equivalent. I disagree and would suggest that more comparative data are needed that has objective measureable outcomes. As such it should be an area recommended for future research. 3) I do not believe the data is strong enough to conclude that TKR requires extended prophylaxis (Question 8).	Thank you for these considerations. Regarding the DTI and Xa inhibitors, please see the response above to explain inclusion of individual drug agents. Regarding key question 6, please see the response, 2 above from this comment. Regarding key question 8, please see the response above marked #11 under results.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1	Executive Summary	I must preface my comments by saying that I glanced through the draft yesterday but cannot fully download either the draft report or the appendixes today despite several attempts. I am writing based on my Executive Summary review of yesterday. Executive Summary and Table 7: The findings are misleading as presented. The PE incidence in hip replacement looks unusually high (6%, page 19). It is important for the EPC authors to determine and inform readers how the hip replacement population in the very limited number of hip replacement RCTs (5) differs from the TKA and hip fracture patients, since the findings are not remotely in line with clinical expectation. The 6% PE finding borders on alarming and unbelievable. We would expect hip fracture patients to have the highest PE incidence, followed by TKA (lesser), with hip replacement at or below the TKA PE incidence level. Although I do not have (and cannot easily obtain) the 4 RCTs from the 1980's, my first thought is that the hip replacements in the 1980's articles included a large number of cancer patients. Metastases and non-hip, non-bone cancer patients have a much higher risk of PE than elective arthroplasty patients, and many cancers metastasize to the hip. It is incumbent upon the EPC to identify these and other differences that could account for such an unexpected estimate, rather than homogenizing and reporting, "The percent of patients with malignancy ranged from 0 to 7.14%" (page 18). Were the PEs in the cancer patients? What other medical, injury or treatment factors (i.e. orthopaedic resident cases, time?) are driving the estimate? Also, the EPC authors state (top, page 19) that 5 RCTs were used for the pooled estimate of PE in hip replacement (ref 14, 27, 28, 42 and 43) but later state in the text that the Kim article (ref 14) included some bilateral hip replacement patients and was therefore not included in pooled estimates. It would be valuable to note that the 6% estimate is therefore based on 4 articles that were published in 1981, 1982, and 1986 (2) and does not likely reflect "contemporary" risk as suggested on page 18.	Thank you for this comment. We have reviewed the five included trials in the pooled incidence of PE as you have suggested. Of all trials, 1 patient in the placebo group in one trial had a history of malignancy; otherwise no patients had malignancy in the studies which explicitly reported this characteristic. The trial by Modig and colleagues, which had the highest incidence of PE, was conducted in patients with osteoarthritis. Therefore, we do not feel that aside from those factors already identified in the key points, there are others that may be contributing to heterogeneity. We are unclear about the comment made that Kim et al was excluded from the PE analysis. In the report, there is no statement that Kim et al was excluded from the pooled analysis of PE. We state that five trials were pooled and present the result of that pooled incidence. Additionally, the methods states that 1980 to most currently published data was used to define contemporary practice, as agreed upon with the TEP.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 2	Methods	KQ 11: There is a MAJOR flaw in your care pathway. It should not start with the surgery. It should start with an assessment of risk factors 6-12 months before surgery, ie: mobility, airline flights or dehydration pre-op, Protein C deficiency, and other conditions that predispose to DVT that can be assessed with a good pre-op history. Rarely is this done. Patients that are high risk for conditions other than JUST the type of surgery should be anti-coagulated. I had a simple surgery: Morton's Neuroma and Plantar Fascia release but flew 9000 miles for the surgery. I was almost immobile for 6 months pre-op due to the pain. No one considered putting me on anti-coagulants because of the type of surgery. I suffered a saddle embolism of the pulmonary artery and almost died.	Thank you for your comment. We are so sorry to hear of your injury and hope you now doing better. The concerns you raise are reasonable, although a CER is not designed to simulate a care pathway. In a CER, we are charged with determining the balance of benefits and harms, strength of the evidence and applicability. In assessing the applicability of the evidence, the population which is represented by the evidence is taken into consideration (i.e. high vs. standard risk for VTE). We agree that there are other risk factors aside from the type of surgery which may modify the risk of VTE in a patient that may be considered when deciding the balance of benefits and harms. For this reason, we answered key question 2, which addresses the patient characteristics which may alter risk of VTE or bleeding outcomes.
Public Reviewer # 3	General	Venous thromboembolism (VTE), specifically pulmonary embolism (PE) and major deep vein thrombosis (DVT), remains the most common cause of readmission and death after elective total hip and knee arthroplasty, which account for nearly one million procedures each year. Despite recent advances in patient care, fatal pulmonary embolism occurs in 0.1 - 0.5% of these patients. Routine perioperative anticoagulant prophylaxis has been suggested to reduce PE risk, but must be tempered by consideration of bleeding risk following major orthopaedic procedures where hemostasis is uniquely imperfect in the setting of exposed bony surfaces. Substantial variation exists between current clinical guidelines as proposed by professional associations and clinical practice is highly variable. Federal agencies threaten penalties for noncompliance with controversial guidelines and pharmaceutical companies have funded large trials that recommend costly anticoagulants that are not popular in the surgical community because of the associated risk of bleeding complications. Genuine equipoise exists in this clinical arena and there is need for a definitive trial to bring clarity to this important issue. This trial will have great impact on “best practices” relative to venous thromboembolism prophylaxis following total joint replacement by evaluating a balanced approach to prevention of pulmonary embolism that also values avoidance of anticoagulant-related bleeding complications. If the newer agents,	Thank you for this comment. There are several future research needs identified in the report in which large randomized trials would be of benefit.

Commentator & Affiliation	Section	Comment	Response
		studied in clinical trials and advocated by the American College of Chest Physicians (ACCP) and pharmaceutical industry-sponsored practice guidelines, are not found superior to low intensity warfarin or aspirin, the alternative methods supported by the American Academy of Orthopaedic Surgeons (AAOS), the cost savings to the health care system will be substantial. Savings are related both to the direct drug costs as well as the avoidance of reoperations resulting from the more frequent bleeding complications associated with the newer agents. We propose a large (25,000 patients) randomized non-blinded three-group clinical trial with meaningful clinical endpoints and adequate statistical power to allow concurrent study of both effectiveness and safety in a manner that will provide evidence supporting the most rational approach to this clinical dilemma. This study will challenge prevailing clinical dogma promulgated by current guidelines that are very controversial. The objective of the clinical trial is to compare overall effectiveness (all-cause mortality, clinical PE, and clinical DVT resulting in readmission) and safety (major and wound bleeding) of three thromboprophylaxis regimens endorsed by professional associations in a single clinical trial; aspirin, low intensity warfarin (INR 2.0), and rivaroxaban (or an alternative ACCP approved agent), in conjunction with standard of care use of pneumatic compression devices after elective total hip and knee arthroplasty. Our hypothesis is that venous thromboembolism prophylaxis after total hip and knee replacement with warfarin or aspirin will be equivalent to newer ACCP endorsed agents in terms of preventing clinically meaningful pulmonary embolism and deep vein thrombosis while providing greater safety in terms of reduced bleeding complications that threaten the success and durability of the joint replacement. The primary Specific Aims of the clinical trial are; 1) To compare the frequency of clinically meaningful venous thromboembolism (clinical pulmonary embolism and DVT leading to hospital readmission) among three different thromboprophylaxis regimens. 2) To compare all-cause mortality as an aggregate indicator of fatal pulmonary embolism and related	

Commentator & Affiliation	Section	Comment	Response
		bleeding events associated with routine anticoagulant use among the three different prophylaxis regimens. 3) To compare the frequency and nature of bleeding complications (major and wound-related bleeding) among the three different prophylaxis regimens. Relative to effectiveness of each of the three prophylaxis regimens, secondary observations include; a) Analysis of the contribution of "standard of care" pneumatic compression devices. b) Analysis of the contribution of "standard of care" methods of anesthesia. c) Comparison of frequency of thromboembolic and bleeding events between hip and knee patients. The specific aims of the clinical trial planning grant (R34) are to: 1) Establish the research team; including sites with patients to meet recruitment, site PIs, and staff. 2) Specify the roles and site of central facilities such as the data coordinating center and the study treatment randomization center. Develop tools to ensure data consistency and oversight of research. 3) Establish objective diagnostic definitions for clinical endpoints (bleeding events, PE, and sx DVT) 4) Define recruitment strategy including confirmation of proposed inclusion/exclusion criteria 5) Finalize protocol parameters; confirmation of final outcome measures, prophylaxis agents, sample size estimates, use of compression devices, and stratification for type of surgery and anesthetic 6) Formulation and submission of IND to the FDA for anticoagulant agents used in study context 7) Develop Manual of Procedures to ensure standardization of data collection, endpoint determination, and creation of concealed randomization scheme Culmination will be submission of an investigator-initiated application to NIAMS, NHLBI, and/or AHRQ.	
Public Reviewer # 4	General	Lassen MR, Raskob GE, Gallus A, et al. Apixaban or Enoxaparin for thromboprophylaxis after knee replacement. NEJM 2009;361:594-604	Thank you for this article. We have already reviewed this citation for inclusion in this CER, however because apixaban does not have a current FDA approved indication, this drug does not meet inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Alexander P. Danyluk, PharmD. Director, Medical Information Janssen Scientific Affairs LLC	General	Thank you for the opportunity to comment on the Comparative Effectiveness Report for VTE prophylaxis in orthopedic surgery. After reviewing the report, our comments regarding the differentiation of Factor Xa inhibitors and an overview of rivaroxaban clinical trials in VTE prophylaxis are included below for consideration in future reports. Rivaroxaban is currently an investigational product under FDA review for VTE prophylaxis in hip and knee replacement surgery. Differentiation of Factor Xa inhibitors: Across several key questions and summaries in the report, the Factor Xa category includes both injectable and oral agents. The agents in this category differ not only by route of administration but also in mechanism of action and should be differentiated. The antithrombotic activity of injectable fondaparinux is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa.1 Rivaroxaban is a direct factor Xa inhibitor and does not require binding to ATIII. Rivaroxaban binds to factor Xa in the prothrombinase complex, clot-bound factor Xa, and free factor Xa.2-4	Thank you for this comment. At the time of protocol development, the original and updated literature searches, rivaroxaban did not meet inclusion criteria because it did not have an FDA approved indication. Therefore, together with the expert panel, the class of factor Xa inhibitors was structured as is. Since rivaroxaban has been very recently approved, we were unable to update the full report. However, we have added an addendum to the report regarding the four completed phase 3 trials.
Alexander P. Danyluk, PharmD. Director, Medical Information Janssen Scientific Affairs LLC	General	Rivaroxaban trials evaluate relevant efficacy and safety outcomes: Rivaroxaban's clinical trial program for VTE prevention in hip and knee replacement evaluated the efficacy and safety outcomes that are included in the Comparative Effectiveness report such as DVT, PE, major bleeding, minor bleeding, surgical site bleeding, and others. For your consideration in future reviews, a brief summary of the outcomes measured and the trial results are provided below. 5-8 Efficacy and Safety Outcomes for RECORD 1-4 Studies Efficacy Outcomes Primary Efficacy Outcome ● DVT, non-fatal PE, all-cause mortality Main Secondary Efficacy Outcome ● Major VTE: proximal DVT, non-fatal PE, and VT E-related mortality Other Efficacy Outcomes ● Symptomatic VTE during treatment and follow-up ● DVT: any, proximal, distal Safety Outcomes	Thank you for these comments. Please see the response immediately above.

Commentator & Affiliation	Section	Comment	Response
		Primary Safety Outcome ● Major bleeding starting after the first blinded dose and up to two days after the last dose: Bleeding that was fatal, into a critical organ, or Required re-operation Clinically overt extra-surgical site bleeding associated with a fall in hemoglobin of >2 g/dL or the infusion of >2 units of blood Other Safety Outcomes ● Any bleeding ● Non-major bleeding ● Hemorrhagic wound complications (composite of excessive wound hematoma and surgical site bleeding) Clinical Trial Results: As part of the Phase III RECORD clinical trial program, two randomized double-blind studies (RECORD1 and RECORD2) compared the efficacy and safety of oral rivaroxaban 10 mg once daily to enoxaparin 40 mg SC once daily for VTE prevention in patients undergoing total hip replacement surgery. In RECORD1 the primary efficacy endpoint occurred in 1.1% of patients receiving rivaroxaban compared to 3.7% of patients receiving enoxaparin, (p<0.001). The rate of major bleeding was similar in both groups (0.3% with rivaroxaban vs. 0.1% with enoxaparin; p=0.178). o Hemorrhagic wound complications were reported in 1.5% of rivaroxaban patients and 1.7% of enoxaparin patients. In RECORD2, the primary efficacy endpoint occurred in 2% of patients receiving the extended regimen (i.e., 5 weeks) of rivaroxaban compared to 9.3% of patients receiving the short-term regimen (i.e., 2 weeks) of enoxaparin, (p<0.0001). Major bleeding occurred in 0.1% of patients in both treatment groups. o Hemorrhagic wound complications were reported in 1.6% of rivaroxaban patients and 1.7% of enoxaparin patients. As part of the Phase III RECORD clinical trial program, two randomized double-blind studies (RECORD3 and RECORD4) compared the efficacy and safety of oral rivaroxaban 10 mg once daily to enoxaparin 40 mg SC once daily (RECORD 3) or 30 mg BID (RECORD 4) for	

Commentator & Affiliation	Section	Comment	Response
		VTE prevention in patients undergoing elective total knee replacement surgery. In RECORD3, the primary efficacy endpoint occurred in 9.6% of patients receiving rivaroxaban 10 mg once daily compared to 18.9% of patients receiving enoxaparin 40 mg once daily (p<0.001).The rate of major bleeding was similar in both groups (0.6% with rivaroxaban vs. 0.5% with enoxaparin; p=0.77). o Hemorrhagic wound complications were reported in 2.0% of rivaroxaban patients and 1.9% of enoxaparin patients. In RECORD4, the primary efficacy endpoint occurred in 6.9% of patients receiving rivaroxaban 10 mg once daily compared to 10.1% of patients receiving enoxaparin 30 mg BID (p=0.012). The rate of major bleeding was similar in both groups (0.7% with rivaroxaban vs. 0.3% with enoxaparin; p=0.11). Hemorrhagic wound complications were reported in 1.4% of rivaroxaban patients and 1.5% of enoxaparin patients. We appreciate the opportunity to provide comment. Should any clarification be required on the above, we are available for discussion. References: 1. Arixtra® (fondaparinux sodium injection) [package insert]. Research Triangle Park, NC:GlaxoSmithKline; 2011. 2. Weitz JI, Bates SM. New anticoagulants. J Thromb Haemost 2005;3:1843-1853. 3. Depasse F, Busson J, Mnich J, et al. Effect of BAY 59-7939–a novel, oral, direct factor Xa inhibitor–on clot-bound factor Xa activity in vitro. J Thromb Haemost 2005;3(Suppl 1):Abstract P1104. 4. Perzborn E, Strassburger J, Wilmen A, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939–an oral, direct factor Xa inhibitor. J Thromb Haemost 2005;3:514-521. 5. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-2775. 6. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for	

Commentator & Affiliation	Section	Comment	Response
		the prevention of venous thromboembolism after total hip arthroplasty: a double blind, randomized controlled trial. Lancet 2008;372:31-39. 7. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358(26):2776-2786. 8. Turpie AGG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty: a randomised trial. Lancet 2009;373:1673–80.	
Christopher Dezii	Methods	KQ 4: The Bristol-Myers Squibb Company appreciates ongoing efforts by AHRQ's Effective Healthcare Program to organize knowledge on topics of importance to the health of Americans, including the creation of Technical Assessment Reports addressing areas such as Venous Thromboembolism Prophylaxis in Orthopedic Surgery. We request the inclusion of an analysis of the relationship between acute post-surgical bleeding and re-hospitalization and re-operation along with the planned health outcome analyses.	Thank you for this suggestion. The key questions that are addressed in the CER are pre-defined in collaboration the technical experts during the development of the protocol, which also was publically reviewed. Although this may be an area of interest, at this time the key questions have been defined.
Christopher Dezii	Methods	KQ 11: See response to question 10. Same problem with treating all elective spine surgery the same. Use of VTE, particularly chemical, affected by whether decompression done or not, and magnitude of surgery as well as whether its anterior vs. posterior vs. both.	Thank you for this comment. We agree that "other orthopedic surgery" is a broad term and for that reason, the inclusion criteria for the specific surgeries are detailed in the protocol, methods section.
Belinda Duszynski	Methods	KQ 11: As written, the question appears to treat all elective spine surgeries the same, whether multilevel or not, long deformities, anterior or posterior surgery, decompression, etc. The term elective spine surgery needs to be better defined, as some elective procedures are complex, like deformity, and incur different risks. The North American Spine Society has developed an evidence-based clinical practice guideline that discusses the available evidence regarding use of antithrombotic therapies in elective spine surgery, and can be accessed at: http://www.spine.org/Documents/Antithrombotic_Therapies_ClinicalGuidelines.pdf	Thank you for this comment. We agree that "other orthopedic surgery" is a broad term and for that reason, the inclusion criteria for the specific surgeries are detailed in the protocol, methods section.
Mary Forte, PhD, DC	Executive Summary	See attached	Thank you for this comment.
Health and Science Policy Committee	Executive Summary	Please see attached response.	Thank you for this comment.
Kay Jewell	Methods	KQ 3: White (2003) provides an analysis of	Thank you for this comment which will be considered during

Commentator & Affiliation	Section	Comment	Response
		symptomatic VTE after different surgical procedures, including rates of VTE within 90 days and rehospitalization rates. Total hip arthroplasty and invasive neurosurgical procedures had the highest incidence of VTE, despite that fact that many also had inpatient prophylaxis. They also had the highest incidence of diagnosis after discharge. 56% of VTEs were diagnosed after discharge from the hospital. Total hip (n=56720. LOS – 5.8 da) 91-day VTE rate 2.4%, % after discharge – 1.8% Total knee (n-=65,745. Ave LOS 5.6 da), 91-day VTE rate 1.7%, % after discharge – 0.8% Mohamed (2003)VTE rates within 90 days of Primary total hip: Readmission to hospital – 4.6%, PE, 0.93%, wound infection 0.24%. Spyroupoulos 2009 – (n=41,139 orthopedic cases; managed care, 2001-2005 data) The rate of VTE for orthopedic surgery: 3.5%. DVT alone – 2.5%; PE alone – 1.1%; both PE and DVT – 0.1%. LOS- 4 days. Number of events diagnosed in index hospitalization - -.7% Anticoagulant use in 30days after hospitalization: 40.5%. Median time to event: DVT alone – 70 days; PE alone – 46 days; DVT and PE – 31 days. Colwell (2009) "Total joint arthroplasty patients treated with placebo or as controls have, based on studies conducted between 1908 and 2002, a total DVT prevalence of 41% to 85% and a proximal DVT prevalence of 5% to 36% when examined by venography at 7 to 14 days. Prevalence of PE is less certain, but clinical studies have reported a range of 0.9% to 28% for all PE and 0.1% to 2% for fatal PE in control or placebo patients" Studies of the rates of VTE, readmissions and bleeding were reported by Bullano (2005) and Spyropoulos (2007). They reported on primary and secondary diagnosis and did not analyze orthopedic surgery specifically. However, they do identify additional risks of bleeding events relative to VTE events and readmissions for both. Risk Assessment tool – Maynard (2010a) – new tool to address VTE risk and Decousus (2010) – factors associated with bleeding risk. A realistic report on the risks of bleeding, as major or minor events and their sequelae, are an extremely important issue for this CER. Arepally (2010) reported a survey of physicians about prophylaxis, physician attitudes and barriers. They found that 58% of surgeons referred to guidelines	the revision of this report. Although these outcomes were considered by the Technical Expert Panel in the development of the protocol, these outcomes were not felt to be most comprehensive and of most interest to the variety of stakeholders. The focus of this CER was not secondary prevention therefore outcomes such as recurrent VTE were not included.

Commentator & Affiliation	Section	Comment	Response
		most or all of the time. The guideline used most often was the AAOS (80%). The 3 factors most influencing their choice of agents: efficacy in reducing VTE risk (83%), bleeding risk (57%) and need for monitoring (38%). Orthopedic surgeons focus attention on the risk of bleeding and balance it against the risk of PE in clinical practice. Their assessment of the situation is influenced by the current AAOS guidelines. A CER needs to provide a balanced review of the situation and recommendations. A separate question is the rate of VTE events in patients who did receive thromboprophylaxis. Schiff et al reported a 14% breatkthrough rate. The factors that predicted VTE were Total Knee Replacement (TKR) surgery and type of LMWH used. (Schiff 2005) Additional Outcomes to Consider in the CER: This question refers to the overall risk of VTE and the document lists a number of outcomes related to VTE. There is no question or place to comment on additional outcomes that should be considered in the CER so we will do so here. ACCP offered their response to the AAOS guideline and identified key points with support from the literature. (Eikelboom, 2009) There is no need to repeat their work here. The focus is on the prevention of VTE – both DVT and PE, which have immediate health consequences that prophylaxis is designed to prevent. While the impact of the acute phase of PE and DVT events is important, there are also intermediate and long-term consequences to be considered in a CER. These are not only burdensome to the patient, they also have clinical and socioeconomic ramifications. In addition to post-thrombotic syndrome, which the draft questions have identified, we would add recurrent VTE events as well as a complex regional pain syndrome. Research is also identifying additional association between VTE, acute arterial cardiovascular events . In the Danish study, patients with VTE had a two-fold increased risk for myocardial infarction and stroke during the first year. Becker (2009) addressed these issues with support from literature published since 2007. Becker RC. The importance of VTE prevention after orthopaedic surgery. Lancet. 2009 May 16 2009; 373(9676):1661-1662. Ashrani AA, Heit JA. Incidence and cost burden	

Commentator & Affiliation	Section	Comment	Response
		of post-thrombotic syndrome. J Thromb Thrombolysis 2009; published online Feb 18. DOI:10.1007/s11239-009-0309-3 (accessed April 28, 2009). Deitelzweig SB, Becker R, Lin J, et al. Comparison of the two-year outcomes and costs of prophylaxis in medical patients at risk of venous thromboembolism. Thromb Haemost 2008; 100: 810–20. Douketis JD, Gu C, Piccioli A, et al. The long-term risk of cancer in patients with a first episode of venous thromboembolism. J Thromb Haemost 2009; 7: 546–51. Hsu ES. Practical management of complex regional pain syndrome. Am J Ther 2009; 16: 147–54. Nutescu EA, Shorr AF, Farrelly E, et al. Burden of deep vein thrombosis in the outpatient setting following major orthopedic surgery. Ann Pharmacother 2008; 42: 1216–21. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol 2009; published online Feb 12. DOI:10.1111/j.1365-2141.2009.07601.x (accessed April 28, 2009). Shbaklo H, Holcroft CA, Kahn SR. Levels of infl ammatory markers and the development of the post-thrombotic syndrome. Thromb Haemost 2009; 101: 505–12. Sorensen HT, Horvath-Puho E, Pedersen L, et al. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. Lancet 2007; 370: 1773–79. Turpie AGG, Lassen MR, Davidson BL, et al, for the RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009; published online April 30. DOI:10.1016/S0140-6736(09)60734-0. Zhu T, Martinez I, Emmerich J. Venous thromboembolism: risk factors for recurrence. Arterioscler Thromb Vasc Biol 2009; 29: 298–310.	

Commentator & Affiliation	Section	Comment	Response
Kay Jewell	Methods	KQ 2: The studies on predictors and patient characteristics identify a number of risk factors. The NICE report addresses this in detail with analysis of the studies. Since those publications, there have been additional studies on risk and risk assessment. Maynard (2010a) and Decousus (2010) – factors associated with bleeding risk. A separate question is whether there are patient risk factors associated with VTE events in patients who did receive thromboprophylaxis. Schiff et al looked at this question for major orthopedic surgery. They reported there were no patient characteristics (e.g. previous VTE, malignancy, hormonal therapy or postoperative complications) associated with VTE rates. (Schiff 2005)	Thank you for these comments which will be considered while revising this report.

Commentator & Affiliation	Section	Comment	Response
Kay Jewell	Methods	KQ 3: There are numerous clinical studies cited in the ACCP response to the AAOS (Eikelboom, 2209), in the ACCP guideline (Geerts 2008), in the NICE guideline (NICE, 2007) that address the issue of surrogates for PE. The point is that the focus of the outcome study should not just be PE, symptomatic or fatal. DVT is important not only as a surrogate for PE. While physicians may not consider DVTs to be as serious as a PE, DVTs are a significant clinical event when they occur alone. It is important as an outcome by itself. DVTs occur at a higher rate than PEs as primary and secondary diagnoses. (Spyropoulos 2007) They have a different rate of recurrence, hospitalization, readmission and cost of care. They occur more often than PE in most cases and specifically with TKR (Bjornara, 2006). DVTs require much the same approach as a PE and have the same impact on the patient in the diagnosis and management of the acute event. ; first, they require diagnostic evaluation. Because more than 50% of them occur after hospitalization, there is an office visit/ED visit and often a readmission to the hospital. A DVT must also be treated for 3-6 months. That treatment, as with treatment for PE, usually with warfarin, carries with it its own risks of bleeding, falls, and readmission. It also requires weekly blood testing, dietary adjustment and alteration of habits to accommodate the increased risk of bleeding. DVT also has its own rate of recurrence and complications, e.g. post-thrombotic syndrome and regional pain syndrome. Spyropoulos et al reported that recurrent DVT cost was 21% greater than the cost of the initial DT event (PE costs were the same for the initial and recurrent events). (Spyropoulos 2007) Nutescu (2008) specifically looked at the outpatient burden of DVT following orthopedic surgery. It was associated with a 22% and 74% increase in office and ED visits in the 6-months after discharge.	Thank you for these comments. We included both symptomatic and asymptomatic events as well as DVT and PE events. This is done so that the CER satisfies the needs of a variety of stakeholders including clinicians, patients, and policy decision makers. As such, a more inclusive approach will allow each stakeholder group to have the information that they need to make informed health choices.
Kay Jewell	Methods	KQ 4: The impact of VTE prevention must not focus only on the prevention of symptomatic PE, as the AAOS guideline does. While clinicians and patients want to avoid symptomatic and fatal PE as the most significant outcomes, DVT must also be included in the evaluation, not just as a surrogate for PE but as a distinct clinical entity. ACCP offered their response to the AAOS guideline and identified key points with	Thank you for these comment, please se response immediately above.

Commentator & Affiliation	Section	Comment	Response
		support from the literature. (Eikelboom, 2009) There is no need to repeat their work here. The AAOS recommendations only balance the risk for a symptomatic PE and bleeding. As Deitelzweig (2008) points out, the orthopedic surgeons are focusing on what they see while the patient is in the hospital. The majority of the VTE events happen when they patient has been discharged. The patient probably does not go to the orthopedic surgeon for the symptoms; they go to the ED or their primary care physician. They may be in another town or state. The patient might be admitted to another facility. The surgeon is would not be aware of the rate of the VTE events. What the physician sees in the immediate days in the hospital is the risk of bleeding with its potential impact on the surgery. In discussions with surgeons, bleeding is almost equated with infection which is a surrogate for removal of the prosthesis, as dreaded a consequence for the orthopedic surgeon as a fatal PE. This should not be taken lightly because it is a significant issue for the clinician impacting their decision-making, underestimating the risk of PE and the importance of DVT as a separate entity and the risk with the surgery and overestimating the rate and impact of infections. It can constitute a barrier to appropriate use of prophylaxis if it is not addressed. Thromboprophylaxis and the risk of infection cannot be fully evaluated unless the following are addressed: 1) the relationship of bleeding, wound drainage, and infection to the type of surgical procedure (standard vs minimally invasive) 2) the risk factors for infection and their relationship to thromboprophylaxis, 3) the severity of infection and treatment required including rehospitalization and debridement, and 4) the type, rate and risk factors for infection that requires removal of the prosthesis. A separate consideration is whether the risk of infection can be clinically identified and intermediate steps taken to prevent it. Surgical Procedure issues. In the past 10 years, minimally invasive techniques (MIT) have been developed for TKA. There is a smaller skin incision and more blunt dissection with these procedures. Khanna (2009) and Cheng (2009) reviewed the literature to identify key differences between the procedures, e.g. the length of procedure time/tourniquet time, blood loss	

Commentator & Affiliation	Section	Comment	Response
		and rate of complications. Both reported the blood loss to be about the same or reduced with the MIT. Khanna reported a delayed wound healing problem with the MIT group, thought to be possible due to excessive retraction during the procedure to improve visualization. The rate of superficial infections was 1-4% in the standard group and 0.7-0.8% in the MIT. The rate of deep infections was 1.3% in the standard and 0.2-1.3% in the MIT. The bottom line is that the rate of infections with either technique is much lower than the VTE rate. Infections, risk and management: Saleh (2002) • Risk factors for predicting SSI – (patients did receive prophylactic antibiotics at time of surgery) (Saleh) ? Hematoma (OR= 11.8) ? Days of post-operative drainage (OR=1.32) • Days of drainage (Saleh) ? In noninfected patients, the median time was 2.0 days ? For those patients who developed infection, the median time was 5.5 days Infected Cases Control Received anticoagulants 73% 81% Hematoma 58% 6% Other sites of infection 21% 5% Received blood transfusion 33% 22% • One approach described by Saleh: Patients with hematoma or persistent drainage in excess of 7 days receive IV antibiotics and surgical debridement of the wound if needed. Factors Associated with Prolonged Wound Drainage (Patel 2007) • THA – Factors associated with a prolonged time until post-op wound is dry ? Obese or Morbid obesity ? Use of LMWH (compared with aspirin and mechanical device) ? Higher drain output • Infection rate THA TKA Women 1.2% 0.6% Men 1.0% 0.3% • The difference in drainage based on anticoagulant use was significant on post-op day 5 but not by day 8. Prolong drainage was associated with increased LOS. • There was no significant association between mean postoperative drain output volume and type of prophylaxis. • THA - Prolonged drainage was associated with higher rate of infection when compared to risk with TKA ? “The risk of postoperative wound infection was significantly higher for patients who had prolonged wound drainage after THA and this risk was independent of the type of prophylaxis against deep venous thrombosis. “ • TKA – ? Increased drain output was the only significant risk factor in TKA. ? Obesity was the only independent risk factor associated with a higher rate of infection	

Commentator & Affiliation	Section	Comment	Response
		Minnema (2004) reported on risk factors for SSI with primary TKA between 199-2001. The rate of infections were 0.95%, 1.07% and 1.19% per year. There were a total of 22 infections: 6 superficial and 1 deep and 5 organ-space (prosthetic joint) requiring prolonged antibiotic therapy and additional surgical procedures. The variables independently associated with infection were the use of closed suction drainage less than 24 hours in 90% of cases and an increased postoperative INR (>3). Patients received cefazolin prophylaxis within 1 hour of surgery. They looked at BMI, age, gender, ASA score, comorbidities, medication including the use of steroids, Glucose. OR, surgeon, surgical and tourniquet time, device, cement, estimated blood lost, transfusions as well. SooHoo (2006) reported on complication rates after TKA (90 days after discharge). They reported a readmission rate for infection of 0.71% and PE of 0.41%. [It should be pointed out that the VTE rate is PE only. They did not include DVTs. The data is that DVTs occur at a higher rate in TKA than PEs. The rate for VTE complications would be higher if DVTs were included.] Wound Infections Cases – (numbers of surgery - THA – 1211, TKA – 1226)(Patel, 2007) • THA - 15 patients developed wound infection out of 1211 patients (1.2%) ? Cellulitis in 5– resolved with antibiotics only ? Other 10 patients – required IV antibiotics and after 3 days, irrigation and debridement ? Required removal of the component - 0 • TKA - - 10 infections out of 1227 patients (0.8%) ? Cellulitis in 7 - resolved with antibiotics ? Required operative irrigation and debridement in 1; did not have to remove component ? Infection required component removal – 2 (0.15%)	
Kay Jewell	General	KQ 5: The NICE report addresses this in detail with literature and analysis. A literature search would identify additional comparison studies.	Thank you for these comments. We feel that our literature captured all pre-specified class comparisons relevant to this key question.

Commentator & Affiliation	Section	Comment	Response
Kay Jewell	General	KQ 6: The NICE report addresses this in detail with literature and analysis. There are new articles also. Merli and Groce have recently published an analysis of the different agents, their pharmacologic and clinical differences between the LMWH and implications for prescribing and therapeutic interchange (Merli 2010). Mechanical Devices: A critical practical matter to address with the mechanical devices is compliance and duration of use. Because of patient comfort with them and logistics of reapplying them after ambulation and trips to the bathroom, they are often not applied consistently throughout the day. In its application of VTE protocols, UC-San Diego team audits revealed a 55% rate of compliance with their use, making them ineffective options for thromboprophylaxis. (AHRQ, 2008) The time/effort of nursing to achieve adequate compliance must be considered in addition to the patient factors with compliance. A recommendation for intermittent compression devices as a viable option must include specific recommendations for the amount of time during the day that they must be applied to be effective in reducing the VTE rate. If that threshold cannot be consistently met, then the physician/hospital should not consider them as viable options to reduce VTE events in their facility. UFH: Although unfractionated heparin (UFH) is not recommended as a single option (ACCP 2008), if the CER is going to address its use and effectiveness, the evaluation should pay special attention to the dosing. The effectiveness is different for a dose of twice a day versus three times a day. The difference in dosing and its impact on outcomes is noted in the current guidelines and in the AHRQ and SHM recommendations: Preventing Hospital -Acquired VTE: Guide for Effective Quality Improvement. USCD noted that patients were still getting VTE with the BID dosing. (AHRQ, page19) In its process of developing protocols for VTE prevention, Emory noted a difference in outcome between the two doses. (AHRQ, page 21)	Thank you for this comment. The pre-defined key questions defined between and within class comparisons, but not to the level where different dose regimens were considered separately or evaluated against each other. We did not feel subgroup analyses were necessary given the results found from the primary base case analyses, based on drug regimen.
Kay Jewell	General	KQ 7: The NICE report addresses this in detail with literature and analysis. Compliance for the mechanical modalities remains a factor. (see #6)	Thank you for these comments which were considered when assessing the applicability of the evidence.
Kay Jewell	General	KQ 8: There is a more fundamental issue with this question. The question compares 7 day with 30 days or	Thank you for these comments which will be considered while revising this report. CERs are designed to determine

Commentator & Affiliation	Section	Comment	Response
		longer prophylaxis. It should be pointed out that patients are generally not receiving even 7 days of prophylaxis. The hospital stay has been decreasing and patients have not been receiving the 7 day prophylaxis that is used and reported in the clinical studies, e.g. for enoxaparin. Most patients are receiving prophylaxis only during their hospital stay. • 2003 – Ave LOS – hip – 5.8 days, knee – 6.3 days (White, 2003) • Huo (2009) – reports the trend to lower LOS for total hip and total knee, from 4.7/4.5 days respectively in 1996 to 3.7 days for both in 2001 • Spyroupolous 2009 data reported less than 40% of orthopedic patients received anticoagulants after the index hospital stay. • The SCIP-VTE 1 and 2 measures, which apply to high risk surgical procedures including major hip/knee procedures, do not apply if the hospital stay is less than 3 days. If clinicians use that as their guide, many patients may not even receive prophylaxis during their hospital stay. Extended prophylaxis after 7 days: The ACCP and NICE guidelines address this with supportive literature cited – they recommend extended prophylaxis for major orthopedic surgery. The incidence of VTE is lowest with the longest duration of prophylaxis (Eriksson 2003). Rates of VTE ranged from 5.2% to 11.7% in patients treated for 9 to 11 days, from 6.7% to 13.4% in patients treated for 6 to 8 days, and from 8.7% to 17.0% in those treated for <=5 days. Repeated studies report that most of the VTE events are diagnosed after discharge from the hospital. White reported that 56% were diagnosed after discharged (all surgeries). Total or partial hip arthroplasty had the highest rate of diagnosis after discharge. Huo & Muntz summarized the literature on the need for extended prophylaxis (Huo 2009). They cited the following: • White (2003) The diagnosis of VTE was made after hospital discharge in 76% of THRs and 47% of TKRs, and the median times to diagnosis were a respective 17 and 7 days. • Bjornara (2006) - 71% of symptomatic DVTs and 61.8% of symptomatic PEs occurred after discharge. • Schelling (2005) median time to diagnosis after THR and TKR is 17 days and 7 days respectively. • Dahl (2000) – mean duration to VTE symptoms was 27 days for THR. 17 days for TKR and 36 days for hip fracture. Eikelboom (2001) – reported that extended	comparative effectiveness which includes the balance of benefits to harms, the strength of evidence, and applicability of evidence. CERs are precluded from using cost as a factor in determining comparative effectiveness. The length of VTE prophylaxis used in trials was taken into consideration when evaluating the applicability of the evidence.

Commentator & Affiliation	Section	Comment	Response
		duration of thromboprophylaxis was not associated with major bleeding although there was an increase in minor bleeding. Experience with bleeding with extended prophylaxis for other surgeries; in the ENOXACAN study, there was not an increase in bleeding (Bergqvist 2002) The shorter hospital stays and need for prophylaxis in the outpatient setting create new issues for patient care. There is a need for sufficient days to allow for bridging between LMWH and warfarin, reimbursement for medications in the outpatient. Another major factor is the transition of care from the hospital to the outpatient setting with appropriate connection with the clinic that will educate the patient on anticoagulation, provide the testing, monitor for side effects and adjust doses when necessary. Outpatient appointments within 7 days of the discharge will facilitate adherence to medication use and testing. The analysis for extended use should consider not only the effectiveness on reducing VTE events and the risk of major and minor bleeding, it should also consider all the costs associated with each drug. This would include the direct medical costs of the drug, lab testing, and office visits, ED visits, and readmissions for VTE and bleeding events, long-term VTE costs as well as the indirect costs to the patient of time lost from work/life for events and for lab testing and appointments as well as patient health-related QoL issues associated with each drug. ADDITIONAL REFERENCES: Bergqvist D, Jo¨nsson B (1999) Cost-effectiveness of prolonged administration of a low molecular weight heparin for the prevention of deep venous thrombosis following total hip replacement. Value Health 2:288–294. doi:10.1046/j.1524-4733.1999.24003.x Dahl OE, Pleil AM (2003) Investment in prolonged thromboprophylaxis with dalteparin improves clinical outcomes after hip replacement. J Thromb Haemost 1:896–906. doi:10.1046/j.1538-7836.2003.00236.x Friedman RJ, Dunsworth GA (2000) Cost analyses of extended prophylaxis with enoxaparin after hip arthroplasty. Clin Orthop Relat Res 370:171–182. doi:10.1097/00003086-200001000-00016	
Freda C. Lewis-Hall, MD Chief Medical	General	Pfizer is pleased to submit comments in response to the Agency for Healthcare Research and Quality's (AHRQ) request on draft key questions on the	Thank you for this comment. CERs are designed to determine the comparative effectiveness of different interventions. This includes determining the balance of benefits to harms,

Commentator & Affiliation	Section	Comment	Response
Officer, Pfizer		"Comparative Effectiveness of Venous Thromboembolism (VTE) Prophylaxis in Orthopedic Surgery." Pfizer is both a global leader in life sciences and a research-based organization with extensive clinical expertise in VTE. We applaud the efforts AHRQ is undertaking to develop evidence reports and technology assessments to assist patients and physicians in their decisionmaking regarding prevention of VTE in patients undergoing orthopedic surgery. Pfizer agrees that a cmprehensive evaluation of both pharmacologic and mechanical strategies to prevent VTE in orthopedic surgery patients is important given that deep venous thrombosis (DVT) occurs in orthopedic surgery patients at a much higher rate than general surgery or other medical patients, and it can lead to serious outcomes such as pulmonary embolism (PE), bleeding, and death. To that end, we submit the following recommendations to improve the structure, clarity and specificity of the analysis: Structure analysis and report to ensure findings are clinically appropriate and reflect the availability of evidence. The key questions take a comprehensive and detailed approach to assessing evidence on both pharmacologic and non-pharmacologic interventions for VTE across a wide range of outcomes. In addition, we recommend the evidence be evaluated and the report be structured in concordance with actual care delivery to ensure the review's findings are clinically relevant. Specifically, Key Questions 1 – 9 address patients undergoing "major orthopedic surgery" (MOS), grouping total knee replacement (TKR), total hip replacement (THR), and hip fracture surgery together as one group. However, the availability of evidence and the findings may vary among these types of surgery. Therefore, we recommend the assessment consider each type of MOS separately. Similarly, Key Questions 10 and 11 group distal to knee injuries, conditions requiring knee arthroscopy, with elective spine surgery as examples for "other orthopedic conditions." Since the impact of treatment may vary depending on the patient's orthopedic condition, we recommend AHRQ stratify its	assessing the strength of evidence, and determining the applicability of evidence. So we have summarized the available evidence and rated the strength of evidence. In the proposed methodology to the TEP, we recommend that the three surgeries (total hip replacement, total knee replacement, and hip fracture surgery) be analyzed together as "major orthopedic surgery" as well as individually. By pooling all the orthopedic surgeries together, it enhances power to detect differences between interventions and we can assess for statistical heterogeneity which will give us an indication of whether the surgeries can be pooled together. Because of known clinical heterogeneity, arising from the different procedures, we also analyzed each surgery separately (total hip, total knee, and hip fracture) in subgroup analyses and reported the results of these subgroups. We agree that the population included in "other orthopedic conditions" required further specification and we have specified the three broad surgical categories within the key questions and further defined them within the methods of the protocol. Please see above regarding the comment of pooling surgeries together.

Commentator & Affiliation	Section	Comment	Response
		evaluation across each orthopedic condition considered. Doing so will ensure that the available evidence is assessed in the appropriate clinical context and will provide clarity in results and conclusions.	
Freda C. Lewis-Hall, MD Chief Medical Officer, Pfizer	Methods	Clarify definitions of key terms (i.e., patient outcomes, VTE, and bleeding outcomes). Several of the draft key questions address similar outcomes, but they are not consistently or clearly defined across questions. Since published clinical trials have used a variety of definitions for some outcomes, which adds to the difficulty in comparing data between studies, Pfizer recommends that the key questions apply a consistent definition for each outcome considered and that these definitions are clearly stated throughout. For example, Key Question 3 provides no definition for "important patient outcomes," a term that could be interpreted differently by stakeholders depending on their experience and level of expertise. We recommend this phrase be clarified, particularly as to how these "important patient outcomes" will contrast against the surrogate outcomes Key Question 3 addresses. Key Questions 1 and 2 also do not provide a definition for VTE, while subsequent questions define it as: "Asymptomatic or symptomatic, proximal or distal deep venous thrombosis (DVT) detected by venography or ultrasound, proximal DVT, non-fatal pulmonary embolism (PE), fatal PE, symptomatically objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)." If VTE in Key Questions 1 and 2 is meant to be defined in the same way as in subsequent key questions, we recommend this definition be stated in each question to avoid confusion or it be stated that this is the intent across all questions. Similarly, "bleeding outcomes" are not clearly defined in Key Questions 1 or 2, while subsequent questions define "bleeding" as "major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion." Pfizer recommends that AHRQ also include clinically relevant non-major (CRNM) bleeding and clarify whether this definition is intended to be used for Key	Thank you for this comment. The wording of key question 3 was changed and no longer states "important patient outcomes". We would like to clarify that the term VTE, when used in the listing of outcomes within key questions, collectively refers to the various DVT and PE outcomes that will be analyzed independently, as depicted in the analytic framework under intermediate and final health outcomes. The term "bleeding", when used in the listing of safety outcomes within each key question, collectively refers to all of the individual bleeding outcomes that we propose to analyze independently. To account for the potential variability in the definitions used in trials to define particular outcomes, we tested for statistical heterogeneity for each outcome analysis. Additionally, the definitions used for major and minor bleeding in each trial are include in the evidence tables. Although raised to the TEP, the addition of CRNM as an outcome was not determined to add value beyond the outcomes which were already specified.

Commentator & Affiliation	Section	Comment	Response
		Questions 1 and 2 as well. Further, since multiple definitions exist for some bleeding outcomes (e.g., major, minor, and CRNM bleeding), these terms should be more precisely explained using definitions from a recognized standards-setting organization such as the International Society on Thrombosis & Haemostasis (ISTH).	
Freda C. Lewis-Hall, MD Chief Medical Officer, Pfizer	Methods	Consider pharmacologic and mechanical thromboprophylaxis strategies in this assessment. We recommend that key questions assessing the impact of pharmacologic and mechanical thromboprophylaxis strategies (i.e., Key Questions 4 – 8, Key Question 10, and Key Question 11) take into consideration the dose of thromboprophylaxis and the operating conditions of mechanical interventions. The relative impact or comparative efficacy of therapies may differ based on these factors and they currently do not appear to be considered as part of the evaluation. Explicitly including them in this assessment will be valuable to ensure the analysis includes a full range of interventions that physicians and patients consider in the context of VTE prevention.	Thank you for this comment. We extracted information regarding the dose regimen and operating conditions (duration of use and compliance) when reported in trials although basing analysis on these factors was not included in the protocol. We did consider these factors when statistical heterogeneity was observed in a particular analysis. The data regarding the exact regimen can be found in the quality and characteristics table within the appendix. These factors were considered when assessing the applicability of the evidence.
Freda C. Lewis-Hall, MD Chief Medical Officer, Pfizer	Methods	Refine Key Question 2 to target relevant subpopulations. We recommend that Key Question 2 be further refined to target specific subpopulations that are generally more likely to experience complications during surgery, including patients aged 75 years and older, patients weighing 50 kilograms or less, and patients with renal impairment. Tailoring the evidence assessment in this key question to relevant subgroups will help ensure that findings are most useful and appropriate for clinical decisions frequently made regarding VTE.	Thank you for this comment. The evaluation of special populations such as those suggested in your comment (i.e. patients older than 75 years, patients weighing 50kg or less and patients with renal impairment) is beyond the scope of this CER.

Commentator & Affiliation	Section	Comment	Response
Freda C. Lewis-Hall, MD Chief Medical Officer, Pfizer	Methods	Refine Key Question 8 to account for variation in length of prophylaxis by patient profile and/or intervention type. Pfizer would like to emphasize the importance of assessing the effects of prolonged thromboprophylaxis since the duration of prophylaxis in patients that have undergone THR or TKR is often much shorter than the period in which these patients are at risk for thromboembolic events after surgery.1 Consequently, Key Question 8 should be refined to account for different types of surgery as the length of prophylactic therapy needed may differ by surgery type. Additionally, the 7-day period articulated in this key question may not apply to all interventions. For example, a minimum of 10 days of prophylaxis for TKR was considered for several new agents. The 7-day period currently included in this key question may be inappropriate for the available evidence on certain classes of interest. Therefore, Pfizer recommends the key question be refined to address the variation in recommended duration. In conclusion, we would like to commend AHRQ for addressing this topic and for seeking comment on the draft key questions. We appreciate AHRQ's willingness to partner with healthcare stakeholders, including the life sciences industry, to improve our nation's healthcare. We look forward to seeing our suggestions incorporated into the final key question set. As Pfizer's efforts in this therapeutic area continue, we look forward to further collaboration with the Agency on improving the body of clinical evidence for VTE and other important therapeutic areas. 1 D. Warwick, R.J. Friedman, G. Agnelli, E. Gil-Garay, K. Johnson, G. FitzGerald, F. M. Turibio. Insufficient duration of venous thromboembolism prophylaxis after total hip surgery or knee replacement when compared with the time course of thromboembolic events. The Journal of Bone & Joint Surgery (2007) 89(6): 799-807.	Thank you for this comment. We analyzed the three surgeries (total hip replacement, total knee replacement, and hip fracture surgery) together as "major orthopedic surgery" as well as individually. By pooling all the orthopedic surgeries together, it enhances power to detect differences between interventions and we can assess for statistical heterogeneity which will give us an indication of whether the surgeries can be pooled together. Because of known clinical heterogeneity, arising from the different procedures, we also analyzed total hip, total knee, and hip fracture separately as well and reported results of these subgroups. While a minimum of 10 days of prophylaxis for TKR is a consensus recommendation, the majority of data in the literature is for 7 days of therapy for standard prophylaxis and for over 30 days for extended prophylaxis. We agree with you that it may be more inclusive to define 7 to 10 days as standard prophylaxis to assure that some relevant studies do not get excluded from inclusion in answering this KQ.
Freda C. Lewis-Hall, MD Chief Medical Officer, Pfizer	Methods	Pfizer appreciates the opportunity to submit comments on AHRQ's draft research review on "Venous Thromboembolism Prophylaxis in Orthopedic Surgery." Pfizer is a global leader in life sciences and a research-based organization with extensive clinical expertise in therapies for venous thromboembolism (VTE). We	Thank you for this comment. Apixaban was not excluded because "it is not a comparison of interest" as stated in the comment. Apixaban was excluded because it is not FDA approved for any indication at this time, nor at the time of the original literature search or the updated literature search. The same criterion applied to all interventions evaluated in this

Commentator & Affiliation	Section	Comment	Response
		value AHRQ's continued efforts to develop evidence to inform and support better patient and physician decision making. As such, we respectfully submit the following comments for your consideration to help ensure the research review is relevant to and appropriate for clinical application. Include relevant data from studies on additional prophylaxis anticoagulants, specifically oral Factor Xa inhibitors, to more comprehensively assess available evidence on existing therapies. Currently, the draft research review omits a number of key studies evaluating the comparative effectiveness of different anticoagulant therapies for VTE. Specifically, the report overlooks evidence demonstrating the comparative value of apixaban, an oral factor Xa inhibitor, when used to prevent VTE following elective knee replacement surgery. While we recognize that studies of apixaban are currently excluded because they are not "comparisons of interest," we recommend expanding the inclusion criteria to allow for the evaluation of this novel therapy. AHRQ should strive to be consistent in its criteria for determining which therapies are included in the review. While not yet approved by the FDA for use in the U.S., apixaban has recently been approved by the European Medicines Agency (EMA) for use in Europe. This is the same scenario facing rivaroxaban (Xarelto), another oral factor Xa inhibitor, as it does not have FDA approval but is approved for use in Europe. However, the current draft research review does evaluate rivaroxaban. In the interest of applying a consistent approach for determining which therapies are included in its draft report, Pfizer recommends incorporating the following studies to provide a more thorough and accurate overview of the current landscape of VTE therapies: Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med. 2009 Oct 29;361(18):1814. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010 Mar 6;375(9717):807-15.	CER, as such rivaroxaban was also excluded. This is a criteria explicitly determined by AHRQ for CERs.

Commentator & Affiliation	Section	Comment	Response
Freda C. Lewis-Hall, MD Chief Medical Officer, Pfizer	Methods	Incorporate significant studies on oral Factor Xa inhibitors outside of the inclusion cutoff date to offer a more complete assessment of available evidence and avoid omission of key data. We appreciate AHRQ's thorough review of the available evidence and use of clear inclusion and exclusion criteria to determine appropriate evidence for review. However, we recommend considering an extension of the cutoff deadline for published reports to allow for the addition of important data from recent trials on oral Factor Xa inhibitors. The findings from the following study contribute important new data to comparative evaluations of therapies for the prevention of VTE following elective hip replacement surgery and warrant inclusion in the final report. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med. 2010 Dec 23;363(26):2487-98. We appreciate AHRQ's willingness to consider comments from stakeholders and work with relevant healthcare sectors, including the life sciences industry, to improve population health in the United States. We are happy to answer any questions you may have on these comments and to provide additional information as needed.	Thank you for this comment. Modifying the inclusion dates would not allow for inclusion of apixaban since the drug is not FDA approved. Please see the comment above.
Caliann T. Lum, MD, PhD, FACS	Methods	Despite all the work put into this report, I do not think it will be possible to cleanly answer key questions unless patient specific data is extracted, stratified, and analyzed.	Thank you for this comment. Patient level data was not sought for this comparative effectiveness review.
Caliann T. Lum, MD, PhD, FACS	Results	If at all possible it would be helpful to show comparative data in tables so that treatments (eg, pharmacologic, mechanical) could be easily compared across the board with regard to major outcomes, including any comparative statistical results.	Thank you for this comment. We agree that with the number of key questions, there are a number of comparisons being made. For that reason, after each key question we present the data in tabular format, with statistical results, so that the reader can quickly compare the interventions within a key question. For a higher level summary, we have constructed a table that includes all comparisons for all outcomes (regardless of the key question) along with the strength of evidence rating (lo, moderate or high outcomes only). This table appears in the executive summary and well as early in the report.

Commentator & Affiliation	Section	Comment	Response
Caliann T. Lum, MD, PhD, FACS	Discussion	What can be said about the differences in recommendations between ACCP and AAOA? Are they planning to issue a joint recommendation?	Thank you for this comment. The technical expert panel included representatives from both organizations so that their interests were captured for this report. However, we are unsure of the status of these organizations independently in their plans to generate a joint recommendation. This is outside of the scope of the CER.
Jeff Maitland	Methods	KQ 3: Approve with comments. Although the QIC recognizes the pivotal importance of this questions, we question how this will be answered. The QIC noted that AHRQ should think about this question carefully when attempting to answer this question, as it may be based upon expert opinion and strong personal provider preferences. As an alternative, the QIC suggested that AHRQ not focus purely on mortality, but	Like QIC, we felt that this would be a difficult question to answer. An ideal surrogate is correlated to an outcome and an intervention which impacts that surrogate is found to impact final health outcomes of interest. While this level of data did not exists, it is important to summarize what is known so that stakeholders can use this information when determining which outcomes will most impact their healthcare decisions.
Jeff Maitland	Methods	KQ 4: Disapprove with comments. The QIC feels that too many classes are grouped together for these outcomes, making it impossible to separate the "signal from the noise". From a clinical standpoint, a positive result might be helpful, but a negative result would clearly not rule out an important effect.	Thank you for this comment. We analyzed each identified pharmacologic and mechanical class independently and not collectively in one analysis.
Jeff Maitland	General	KQ 5: The QIC wanted to ensure that AHRQ did not use multiple comparisons across classes in their analysis. The QIC agreed that if AHRQ examined the rates of the major outcomes in each class they will be able to find clinically important data.	Thank you for this comment. We only used direct comparisons to answer this key question.
Jeff Maitland	General	KQ 6: Approve with comments. The QIC recommends placing the classes toward the beginning of the research question, so it is easier to understand.	Thank you for this comment. The classes were moved to the beginning of the key question.
Jeff Maitland	General	KQ 7: Approve with comments. The QIC would like to ensure that AHRQ examines the effects ofthe combination of pharmacologic and mechanical modalities versus pharmacological or mechanical prophylaxis alone (not simply "single modality").	Thank you for this comment. You are correct, pharmacologic plus mechanical prophylaxis was compared to either pharmacologic or mechanical prophylaxis.
Jeff Maitland	General	KQ 11: Approved as written	Thank you for this comment.
Stephen Mascioli, MD, MPH Chief Medical Officer Covidien Vascular Therapies	General	As an industry leader in mechanical prophylaxis (intermittent pneumatic compression, venous foot pump, graduated compression stockings), Covidien appreciates the opportunity to respond to the research questions posed by AHRQ on the Comparative Effectiveness of Venous Thromboembolism (VTE) Prophylaxis in Orthopedic Surgery dated May 7, 2010. The clinical problem presented by hospital acquired VTE is multi-faceted, requiring great consideration for the desired cause of prophylaxis, and also for the	Thank you for your support in this effort.

Commentator & Affiliation	Section	Comment	Response
		undesired effects, which make answering the questions difficult. Covidien has chosen to submit this statement that highlights our general position and to begin engagement in this process with the expectation that there will be further dialog as the process moves forward. Appropriate prophylaxis in the Total Hip Replacement (THR), Total Knee Replacement (TKR) and Hip Fracture Surgery (HFS) patient continues to generate much debate. It is important that the flexibility now provided in the ACCP and AAOS guidelines continues to be supported by the NHIQM so that the surgeon is not put at odds with the hospital because of differences in the guidelines and the core measures. In addition, while there is always a need for further clinical evidence, the available data in the THR/TKR patient population remains the most studied patient population where there is the greatest awareness of the problems caused by VTE. The Key Questions read that the goal of this effort is to generate comparative research that is able to reach conclusions that certain prophylactic interventions are better than others. Covidien is committed to the process and wants to ensure that the continuum of patient care, from admission through discharge, and what might be appropriate at specific points in time during a hospital stay, is properly addressed. This position, which is shared by many surgical specialties, is a multi-modal strategy offering patients the best care by minimizing their risk of VTE while simultaneously not escalating their risk for bleeding complications. An example of this strategy would be the use of mechanical prophylaxis intra-operatively and continued until discharge with chemoprophylaxis being added when the risk of surgical site bleeding has subsided or a safe time period has elapsed from the use of spinal or epidural anesthesia. The chemoprophylaxis would then be continued for some period post discharge to address the continue risk of VTE. Therefore, guidance on proposed research would be to fund clinical trials that produce data that give guidance to comprehensive strategies. These strategies would cover what prophylaxis is appropriate at times of varying VTE and bleed risk. 15 HAMPSHIRE STREET 508-452-4974 [T] MANSFIELD, MA 02048 508-261-6015 [F]	

Commentator & Affiliation	Section	Comment	Response
		In conclusion, Covidien is supportive of AHRQ's efforts to provide increased clarity to clinicians on best-practices to eliminate VTE as well as all-cause morbidity and mortality in hospitalized patients. We look forward to future participation with AHRQ and other stakeholders in this collaborative effort.	
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	Methods	KQ 1: a. Data for specific surgeries should be considered separately. It is likely not useful (and may be confounding) to condense these three different surgeries in one group. Total hip, total knee, and hip fractures should be evaluated separately. b. We feel very strongly that the outcome measure for venous thromboembolism should be symptomatic events. In relation to "bleeding outcomes" we are concerned about blood transfusion, return to the operating room, infection, prolonged drainage, prolonged hospital stay, and any loss of function or increase in pain or stiffness because of the bleeding event.	Thank you for this comment. A) The methodology collaboratively determined with the TEP specified pooling of the three major surgeries together to enhances power to detect differences between interventions. Because of known clinical heterogeneity, arising from the different procedures, we also performed subgroup analyses specific to each of the three surgeries separately. B) The methodology specified inclusion of both symptomatic and asymptomatic events and not limiting to symptomatic events only. This was done since CERs have to satisfy the needs of a variety of stakeholders including clinicians, patients, and policy decision makers. As such, a more inclusive approach such as the one we are proposing will allow each stakeholder group to have the information that they need to make informed health choices. Although previously suggested outcomes such as those stated were considered by the Technical Expert Panel in the development of the protocol, they were not ultimately included.

Commentator & Affiliation	Section	Comment	Response
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	Methods	KQ 2: a. Data for specific surgeries should be considered separately. It is likely not useful (and may be confounding) to condense these three different surgeries in one group. Total hip, total knee, and hip fractures should be evaluated separately. b. Timing of surgery and immobilization status should be considered in addition to patient specific characteristics. This should include separate analyses for hospital length of stay (timing of patient discharge after joint replacement surgery) and also timing and extent of mobilization after surgery while the patient is in the hospital. c. Mechanical devices should be evaluated independently. d. We feel very strongly that the outcome measure for venous thromboembolism should be symptomatic events. In relation to "bleeding outcomes" we are concerned about blood transfusion, return to the operating room, infection, prolonged drainage, prolonged hospital stay, and any loss of function or increase in pain or stiffness because of the bleeding event.	Thank you for this comment. A) Please see the response above. B) The suggested characteristics were evaluated for, as there were no restrictions in the methodology as to which specific patient and surgical characteristics would be evaluated. All of the data that was identified through our literature search, regardless of the characteristic, have been presented in the results. C) This KQ evaluated predictors of VTE or bleeding outcomes regardless of the method of prophylaxis. The impact of the method of prophylaxis on VTE and bleeding outcome was evaluated in the other KQs in this CER. D) Please see the response above.
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 3: This is a very important question. Based on research available in independent analyses performed by AAHKS members, we are concerned that this question may not be conclusively answered. We feel strongly that one inclusion criteria for studies in this question should be that patients included should have undergone hip replacement, hip fracture or knee replacement surgery. We feel very strongly that the outcome measure for venous thromboembolism should be symptomatic events.	Thank you for the concerns you raise about this KQ. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. Additionally, each CER report has a section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER. We agree that the population used to answer this KQ is patients undergoing total hip replacement total knee replacement or hip fracture surgery and this was the population evaluated. Regarding the outcomes, please see response above.
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 4: a. Data for specific surgeries should be considered separately. It is likely not useful (and may be confounding) to condense these three different surgeries in one group. Total hip, total knee, and hip fractures should be evaluated separately.	Thank you for this comment. Please see response above.

Commentator & Affiliation	Section	Comment	Response
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 5: a. Dosages for certain LMWH should be examined. b. Dosage, timing, and monitoring recommendations should be incorporated for oral vitamin K antagonists (VKAs). c. Timing and duration should be examined for mechanical interventions. d. The confounding variable of mobilization should be considered. e. Mechanical devices should be evaluated independently. We feel strongly that DVT prophylaxis is not all pharmacologic. f. Timing of surgery and immobilization status should be considered in addition to patient specific characteristics. This should include separate analyses for hospital length of stay (timing of patient discharge after joint replacement surgery) and also timing and extent of mobilization after surgery while the patient is in the hospital.	Thank you for this comment. The exact dose regimen for each pharmacologic therapy was extracted and included in the evidence tables of this CER. Additionally, specific timing and duration of therapy as reported in the study was also included in the tables. Additionally, information such as drug regimen was considered when evaluating the applicability of the evidence. In terms of confounding factors, we evaluated any available literature that was identified by our literature search of the patient or surgical characteristics that may modify outcomes.
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 6: a. This is a very important question. Based on research available in independent analyses performed by AAHKS members, we are concerned that this question may not be conclusively answered	Thank you for this comment. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. In the event where quantitative analysis is not possible for a KQ, qualitative analysis was completed. Additionally, each CER report has a section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER.
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 7: a. Data for specific surgeries should be considered separately. It is likely not useful (and may be confounding) to condense these three different surgeries in one group. Total hip, total knee, and hip fractures should be evaluated separately.	Thanks you for this comment. A) Please see response above.

Commentator & Affiliation	Section	Comment	Response
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 8: a. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy conclusions recommend that patients undergoing THR, TKA, or HFS receive pharmacological prophylaxis for at least 10 days. Why was 7 days chosen by the AHQR? b. For extended prophylaxis the same group suggests intervention for up to 28 to 35 days after surgery. Why was 30 days chosen by AHQR? c. We feel very strongly that the outcome measure for venous thromboembolism should be symptomatic events. In relation to "bleeding outcomes" we are concerned about blood transfusion, return to the operating room, infection, prolonged drainage, prolonged hospital stay, and any loss of function or increase in pain or stiffness because of the bleeding event. d. Based on research available in independent analyses performed by AAHKS members, we are concerned that this question may not be conclusively answered.	Thank you for this comment. While this is a consensus recommendation, the majority of data in the literature is for 7 days of therapy for standard prophylaxis and for over 30 days for extended prophylaxis. The language of the key question defined the shorter duration as 7 to 10 days and the longer duration as greater than 28 days. C) Please see comment above. D) Please see comment above.
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 9: Are there times when a filter and pharmacological prophylaxis are both indicated? Should a filter be ultimately removed? We are specifically interested in the benefits of filter placement and removal in hip fracture patients and patients with a prior history of pulmonary embolism. Data for specific surgeries should be considered separately. It is likely not useful (and may be confounding) to condense these three different surgeries in one group. Total hip, total knee, and hip fractures should be evaluated separately.	Thank you for this comment. We appreciate the questions you have identified. However, as is stated in the report, no literature was found to answer this key question as it is presented.
Brian McGrory MD, Chairman, Evidence Based Medicine Committee, American Association of Hip and Knee Surgeons	General	KQ 10: a. This is extremely broad: "other orthopedic conditions" covers everything. This should be changed to be very specific with each specific clinical scenario defined, e.g. after knee arthroscopy, after spine surgery, etc.	Thank you for this comment. We agree "opther orthopedic surgery" is a broad term and for that reasons the specific surgeries considered in this key question are specified within the question itself as well as in the inclusion criteria section of the methods.

Commentator & Affiliation	Section	Comment	Response
Ian Nathanson, MD, FCCP, Chair On behalf of Health and Science Policy Committee American College of Chest Physicians	General	The American College of Chest Physicians (ACCP) thanks the Agency for Healthcare Research and Quality (AHRQ) for accepting our proposal for an evidence review on thromboprophylaxis in orthopedic surgery to be conducted by The Effective Healthcare Program's evidence-based practice center (EPC) at the University of Connecticut We believe that the effort could have benefited from our expertise in the areas of methodology and content had we been permitted to provide more input than our drafted research questions and initial conversations about estimating baseline risks. A definitive review on this controversial topic could have helped reconcile differences between non-harmonious guidelines and variable practices in this field. Perhaps any future efforts should include developers of the major guidelines in this area, including ACCP. In view of ACCP's excellent track record of using AHRQ reviews as the basis for our guidelines we look forward to future collaborations with AHRQ EPCs.	Thank you for this comment. The Technical Expert Panel for this CER was comprised eight physicians: three provided the orthopedic surgeon's perspective one of which was a local expert, one provided a local pulmonologist's perspective, two provided expertise in methodology/guideline development, one provided a hematologist's perspective, and one provided expertise in health policy. There was equal representation from both the American College of Chest Physicians and the American Academy of Orthopedic Surgeons (three members each).
Vincent Pellegrini	General	KQ 1: These are competing risks of great importance and, somewhat fortuitously, the prevalence of CLINICALLY APPARENT VTE events (PE; 1-2%) is similar to that of clinically important bleeding events (1-3%) with contemporary chemoprophylaxis. This is in contrast to venographic clot prevalence of 5-30% despite use of newer prophylaxis agents. A focus on clinical events allows appropriate powering of a study to simultaneously assess BOTH competing outcome events.	Thank you for this comment which we will consider during the revision process.
Vincent Pellegrini	General	KQ 2: The nature of the operation is the overwhelming risk factor and it dominates any and all specific patient characteristics. However, a past history of PE or clinically apparent DVT despite adequate prophylaxis is an additional risk factor.	Thank you for this comment. We did not limit the patient or surgical characteristics investigated in this key question and have reported data on those identified through our literature search.
Vincent Pellegrini	General	KQ 3: While surrogate outcomes can be measured, they are misleading in the setting of an extended period of prophylaxis as used in the present clinical environment since venographic or other screening methods do NOT accurately predict the occurrence of important clinical events.	Thank you for this comment. We included both symptomatic and asymptomatic events as well as DVT and PE events. This is done so that the CER satisfies the needs of a variety of stakeholders including clinicians, patients, and policy decision makers. As such, a more inclusive approach will allow each stakeholder group to have the information that they need to make informed health choices.

Commentator & Affiliation	Section	Comment	Response
Vincent Pellegrini	General	KQ 4: Prophylaxis is clearly effective in reducing the incidence of both venographic surrogate events as well as clinical VTE events, while concurrently increasing the risk of worrisome bleeding complications. Hence, appropriate use of prophylaxis represents a discussion of a balance between risks and benefits of use of the drug.	Thank you for this comment. The Technical Expert Panelists were in agreement that including a key question (#5) of comparative benefits and harms on between class comparisons was highly applicable to current practice.
Vincent Pellegrini	General	KQ 5: This is the subject of a much needed prospective controlled clinical trial, concurrently considering the relative efficacy of popular agents along with the associated bleeding risk of each intervention. Good comparative information concerning the balance of these risks and benefits is lacking.	Thank you for this comment. In synthesizing the data for key question 5, only direct comparative data was used to obtain the most true comparison between classes of agents in efficacy and safety.
Vincent Pellegrini	General	KQ 6: This information is even harder to come by but the differences are rather modest within intervention classes.	Thank you for this comment. Key questions in a CER should be those of highest importance to the topic rather than those which have the largest volume of literature to answer to question. Determining that there is a lack of evidence or that there is low strength of evidence is of value in CERs.
Vincent Pellegrini	General	KQ 7: There are NO good data to answer this question of relative effectiveness of "stacked" modalities in VTE prevention...despite the common use of such a strategy in clinical practice, drive by a desire to avoid bleeding complications.	Thank you for this comment. Key questions in a CER should be those of highest importance to the topic rather than those which have the largest volume of literature to answer to question. Determining that there is a lack of evidence or that there is low strength of evidence is of value in CERs.
Vincent Pellegrini	General	KQ 11: Mechanical methods may be relatively more effective with distal lower limb clot prevention based on etiology of the thrombosis, as well as instances when bleeding risk is prohibitively high (such as spinal surgery where risk of epidural bleeding is of great concern).	Thank you for this comment. No literature was identified to meet the inclusion criteria for this key question.

Commentator & Affiliation	Section	Comment	Response
Charles Pollack, MD	General	KQ 3: The implication of this question appears to be that DVT – even proximal or symptomatic DVT – is not an "important patient outcome." This implication is given further credence in the "Background" discussion of ACCP vs. AAOS guidelines, wherein the merits of DVT as a "surrogate marker" of PE are discussed. We find this implication deeply troubling. Even though, based on other questions and comments in the text of your draft, we believe you are aware of these, we feel compelled to highlight for a number of reasons: 1) Whether or not it is associated with frank pulmonary embolism, DVT can not be considered a benign condition. It represents a tremendous cost burden to the healthcare system through significantly increased hospital lengths of stay, treatment costs and associated complications (e.g. infection, amputation, and sometimes pulmonary embolism). 2) As many as one-half of patients who develop DVT will develop post-thrombotic syndrome as a direct result, sometimes several years after the instigating episode of DVT. Beyond the well-documented increased risk of repeat thromboembolic events, post-thrombotic syndrome has a permanent impact on quality of life and employability, particularly as we see DVT in younger and younger patients. Thus, the long-term impact of hospital-acquired DVT is at least as consequential as that of non-fatal PE. 3) In short, DVT (or at the very least, proximal DVT) should not be considered merely an "intermediate outcome" or a surrogate marker for PE; rather it should be considered a major outcome endpoint.	Thank you for this comment. The importance of asymptomatic DVT is an area of controversy. While it may increase the risk of PE and post-thrombotic syndrome, asymptomatic DVT would still be considered an intermediate outcome in the analytic framework linked to these other final health outcomes. We have included both symptomatic and asymptomatic events as well as DVT and PE to be evaluated as outcomes so that the CER satisfies the needs of a variety of stakeholders including clinicians, patients, and policy decision makers. As such, a more inclusive approach such as the one we are proposing will allow each stakeholder group to have the information that they need to make informed health choices.
Charles Pollack, MD	General	KQ 5: This question gets to the heart of the "comparative effectiveness" issue, and raises several key competing issues which must be balanced in order to arrive at a sensible conclusion. When is one treatment better than another? When it results in reduced thrombotic event rates? When it is associated with less bleeding? When it doesn't cause immune-mediated thrombocytopenia? When it is cheaper? Clearly a balance must be struck which considers efficacy, safety and cost, but which takes priority? We propose the following rubric: 1, Efficacy; 2, Safety; 3, Cost. Financial considerations cannot be ignored, but two key factors render this a tertiary consideration: First, average hospitalization costs run into the	Thank you for this comment. The decision making scheme you proposed seems reasonable but our CER is not a clinical guideline. In a CER, we are charged with determining the balance of benefits and harms, strength of the evidence and applicability. CERs are precluded from evaluating cost as a determinant of comparative effectiveness. We recognize the variability in the definition used to define bleeding outcomes in the literature. For this reason we have included the definitions of major and minor bleeding used by each trial in the evidence tables and have evaluated different types of bleeding (e.g., major, minor, etc.) separately.

Commentator & Affiliation	Section	Comment	Response
		thousands of dollars per day (much higher still for ICU care), and most agents approved for VTE prophylaxis are relatively inexpensive compared to other drugs or healthcare costs (including ultrasound screening of asymptomatic patients. Thus, acquisition cost is of relatively minor importance except at the extremes. Moreover, differences in less obvious costs such as monitoring, nursing/pharmacy time for administration (IV vs. oral vs. SC) which may counterbalance acquisition costs should be considered. Of far greater consequence is the fact that the costs of treating a DVT or PE (the latter of which, of course, may be fatal) when prophylaxis fails are so high, that preventing only a few events quickly obscures minor differences in acquisition costs. The relative significance of efficacy vs safety is somewhat more difficult to parse. We believe efficacy is the supreme consideration because the known risk of VTE is much greater than the risk of serious adverse events associated with approved therapies. Therefore, when comparing effectiveness to determine whether a strategy should be considered superior to a "standard of care," the following outcomes are possible: 1) Improved Efficacy; Improved Safety 2) Improved Efficacy; No improvement in Safety 3) No improvement in Efficacy; Improved Safety 4) No improvement in Efficacy; No improvement in Safety For outcomes 1-3, the conclusion is that the new strategy is more effective and the relative strength of this conclusion is defined by the numerical order. Assuming there is not an unreasonable cost associated with the new strategy, it should be adopted for the patient population evaluated. For outcome 4, there is no reason to change strategy unless there is a significant cost or ease-of-use benefit. Further, the strength of a given recommendation should be graded based on the strength of evidence supporting the conclusion (i.e. multiple large, randomized clinical trials (RCT) > 1 RCT > registry experience, etc.). This comparative effectiveness concept is deceivingly simple. While there are decades of research which prove the relevance of venography in identifying VTE and predicting outcomes, there is no comparable reference standard for bleeding complications. Large clinical trials are designed and executed using remarkably different definitions of what	

Commentator & Affiliation	Section	Comment	Response
		constitutes “major” or “minor” bleeding, and even introduce variation as to when bleeding is relevant (e.g. excluding “perioperative” bleeding). There appears to be no attempt to arrive at standard definitions, let alone to try to correlate a bleeding definition with outcomes. Whereas in the Cardiology world, the GUSTO classification of bleeding has been shown to correlate closely with morbidity and mortality, no such definition exists for the orthopedic surgery community. This is a glaring weakness for comparative effectiveness research in this arena.	
Charles Pollack, MD	General	KQ 6: This question carries the same issues as question 5 with respect to standardization. Our chief concern with this question is the exclusion of direct thrombin inhibitors from the list of classes to be considered. The direct thrombin inhibitor desirudin is approved for DVT prophylaxis in total hip replacement patients, and other injectable and oral drugs of this class are used in this population – either “off-label” or in patients with suspected immune-mediated thrombocytopenia. This class of agents represents the best alternative for patients with known heparin sensitivity or suspected immune-mediated thrombocytopenia and should be included in the AHRQ analysis. Finally, we wish to express our overall support for the vision of the AHRQ in studying the comparative effectiveness of VTE prophylaxis in orthopedic surgery. Comparative Effectiveness Research (CER) will have a substantial influence on our healthcare delivery system, including reimbursement levels for treatment strategies. Operating in a world of finite resources, we understand the necessity of this approach. However, we also feel compelled to express our desire to ensure that regulatory approval pathways and reimbursement pathways remain parallel. The approval pathway for VTE prophylaxis has been well-defined for many years: demonstrate at least non-inferiority vs. the current standard of care for incidence of symptomatic VTE or venographic endpoints for asymptomatic proximal or total DVT. It may be reasonable to debate whether these are the “best” endpoints, but drug development will cease to be practical if CER results in proposed reimbursement strategies which require different endpoints from those required for approval. For	Thank you for this comment. While desirudin is approved for DVT prophylaxis in total hip surgery, the TEP did not feel that comparing one direct thrombin inhibitor to another would be as important to healthcare decision makers as comparing LMWHs to each other and mechanical devices to each other. If a drug is the only FDA approved agent within a class for that indication, intragroup comparisons have less relevance. Heparin Induced Thrombocytopenia is outside of the scope of this project.

Commentator & Affiliation	Section	Comment	Response
		example, if CER concludes that only differences in PE or mortality are appropriate for choosing a new agent over a prior standard, what use does an "approval" trial which requires expensive venographic identification of venous thrombosis serve? We believe the greatest near-term benefit CER can provide would be to standardize definitions of "safety" for comparison. Recognizing that a small amount of bleeding is likely to occur following major surgery – especially in the presence of anticoagulants – we still have no broadly accepted definition as to what constitutes "serious" or "major" bleeding following "major orthopedic surgery." A standard based on hard outcomes – bleeding-related death, need for re-operation or transfusion would go a long way toward reducing the number of variables in the CER equation. This might also enable more thorough consideration of less common, but still very important safety issues such as immune-mediated thrombocytopenia or other adverse drug responses. For example, if two therapies demonstrated similar efficacy and bleeding-risk profiles, but one agent posed no risk for immune-mediated thrombocytopenia and/or was not contraindicated for patients with thrombocytopenia, how much of an advantage would that represent?	
Tim Schiro	General	KQ 1: The baseline may be difficult to ascertain if the evidence in the literature for VTE incidence (40-60%) is weak. A study population not receiving some form of prophylaxis may be difficult to recruit.	Thank you for this comment. CERs are designed to determine the comparative effectiveness of different interventions. This includes determining the balance of benefits to harms, assessing the strength of evidence, and determining the applicability of evidence. So we will have not only summarized the available evidence we have also provided an assessment of the strength of the evidence.
Tim Schiro	General	KQ 2: The answer to this question may improve VTE prophylaxis and anticoagulant safety by limiting chemical prophylaxis to the highest risk patients (e.g. history of VTE, advanced age, stroke)	Thank you for this comment. We will take these thoughts under advisement as we revise the CER.
Tim Schiro	General	KQ 3: This is an excellent question. The literature suggests that 15% of patients with VTE go on to develop PE, and half of those are fatal. How strong are the studies that support these numbers?	Thank you for this comment. CERs are designed to determine the comparative effectiveness of different interventions. This includes determining the balance of benefits to harms, assessing the strength of evidence, and determining the applicability of evidence. So we will have not only summarized the available evidence we have also provided an assessment of the strength of the evidence.

Commentator & Affiliation	Section	Comment	Response
Teresa Simon	Executive Summary	On behalf of BMS, the summary document did not include 2 of the 3 papers which were published before the cutoff of Sept 2010.(attached as a scientific information package) BMS would like the authors (AHRQ) to consider these publication for inclusion in the draft evidence report of Venous Thromboembolism Prophylaxis in orthopedic surgery	Thank you for this comment. The drug apixaban, since it is not FDA approved for any indication, was not included in this CER. This is a policy of the AHRQ for the completion of CERs.
Teresa Simon	Introduction	see scientific package	Please see response above.
Teresa Simon	Methods	see scientific package	Please see response above.
Teresa Simon	Results	see scientific package	Please see response above.
Teresa Simon	Discussion	see scientific package	Please see response above.
Teresa Simon	List of acronyms/ abbreviations	see scientific package	Please see response above.
Teresa Simon	Tables	see scientific package	Please see response above.
Teresa Simon	Figures	see scientific package	Please see response above.
Teresa Simon	Appendixes	see scientific package	Please see response above.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	General	The American Society of Hematology (ASH) appreciates the opportunity to comment on the Agency for Healthcare Research and Quality (AHRQ) key questions for VTE prophylaxis in orthopedic surgery. The Society represents more than 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases such as thrombosis, leukemia, lymphoma, and anemia. ASH appreciates that the AHRQ recognizes the public health impact of venous thromboembolism (VTE) and that it is focusing on this issue. Below, please find ASH's comments on the key questions that AHRQ proposes to use to address VTE prophylaxis in orthopedic surgery.	Thank you for your comments which we have addressed individually below.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	General	Overall Comments: While there are clearly gaps in the knowledge on orthopedics and thromboembolism, there are also existing evidence-based resources that can save AHRQ time by avoiding duplication of efforts. Specifically, ASH recommends that AHRQ review references 1 and 8 below. For the questions where there is clearly data lacking, it will be useful for AHRQ to review these topics in the context of driving future research. One of the reasons that AHRQ is reconsidering the use of TP in MOS may have arisen from the differences in the recommendations from the 8th ACCP Antithrombotic Guidelines and the document	Thank you for your comments. We were aware of the references you suggested which highlight the difference between the organizations mentioned and considered these points when the protocol for this CER was drafted.

Commentator & Affiliation	Section	Comment	Response
		produced by the American Academy of Orthopedic Surgery. ASH recommends that you also review references 10 and 11 below which compare these two sets of guidelines. The AAOS has stated that it plans to update its guidelines in 2010 and there may be substantial changes. Again, ASH appreciates the opportunity to submit these comments. ASH would be interested in working with the AHRQ on issues related to thrombosis. If you have any questions or require any additional information, please contact ASH Senior Manager of Policy and Practice Carol Schwartz at or 202-776-0544. NOTE: ASH appreciates the assistance of Dr. William Geerts and several reviewers in the development of this document. 1. Geerts WH, et al. Prevention of venous thromboembolism. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:381S-453S. 2. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin. Lancet 2000;355:1295-1302. 3. Lagor C, et al. Weaknesses in the classification criteria for antithrombotic-related major bleeding events. Thromb Haemost 2005;94:997-1003. 4. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-694. 5. Pellegrini VD, et al. Prevention of readmission for venous thromboembolic disease after total hip arthroplasty. Clin Orthop 2005;441:56-62. 6. White RH, et al. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. N Engl J Med 2000;343:1758-1764. 7. Quinlan DJ, et al. Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery. J Thromb Haemost 2007;5:1438-1443. 8. National Institute for Health and Clinical Excellence VTE Guideline Development Group, 2010. Found at: www.nice.org.uk/guidance/CG92.	

Commentator & Affiliation	Section	Comment	Response
		9. O'Donnell M, et al. Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review. Arch Intern Med 2003;163:1362-1366. 10. Eikelboom JW, et al. American Association of Orthopedic Surgeons and American College of Chest Physicians guidelines for venous thromboembolism in hip and knee arthroplasty differ. What are the implications for clinicians and patients? Chest 2009;135:513-520. 11. Struijk-Mulder MC, et al. Comparing consensus guidelines on thromboprophylaxis in orthopedic surgery. J Thromb Haemost 2010;8:678-683.	
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	KQ 1: ASH would like clarification about how "baseline" is defined and assumes that "baseline" means the rates of VTE and bleeding in patients not receiving thromboprophylaxis (TP). If this assumption is correct, ASH does not believe that the baseline rates of VTE can be determined - there are no recent studies that can provide this information since control groups without TP have been considered unethical in major orthopedic surgery (MOS) for more than 25 years.1 Every randomized controlled trial (RCT) done over this time (except for subsets of patients in the PEP trial2) has compared two active interventions. Furthermore, in the clinical trials, highly selected patient groups were used (excluding patients felt to have greater risks of VTE). In addition, surgical techniques, post-operative care and rehabilitation services have changed drastically over the past 25 years. In addition, ASH would like clarification of the definition of "bleeding". There are numerous definitions of bleeding used in the MOS prophylaxis trials with no consensus on which definition is optimal and with limited ability to determine the rates of bleeding using one particular definition if another definition was used in the trial.3,4 For example, whether surgical site bleeding is included or not significantly affects the reported rates of bleeding, and there is no standard definition for what constitutes surgical site bleeding. Furthermore, patients considered to be high risk for bleeding were also excluded from all of the relevant RCTs.	This key question uses the definition of "baseline" as the rate of VTE and bleeding in patients not receiving TP. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. We qualitatively analyze data when quantitative analysis is not possible. Additionally, the report has a section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER. We agree with and recognize that there have been substantial changes in surgical techniques and post-operative care and rehabilitation services over the past years. As such a subgroup analysis of data from 2001- present, defined as May 2011 when the literature search was updated, was conducted. We agree that the definition of bleeding reported in the literature is not standardized and likely varies between studies. Therefore, we reported the definition used in each trial in the evidence tables, for both major and minor bleeding.

Commentator & Affiliation	Section	Comment	Response
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 2: ASH suggests that the question be clarified to refer to VTE and bleeding risks in patients that are receiving thromboprophylaxis. There are studies in MOS patients that have assessed predictors of TP "failures" – i.e. patients who develop VTE despite TP or who develop bleeding while on TP. Although this could be summarized in a systematic review, ASH is unsure of the utility of this question. The rates of clinically-important VTE and clinically-important bleeding are both low in recent MOS clinical trials.1,5 Predictors of asymptomatic deep vein thrombosis (DVT) in MOS include: bilateral arthroplasty, previous VTE, increased age, reduced postoperative mobility, obesity, use of warfarin as prophylaxis, and failure to provide post-discharge prophylaxis.1,6 The studies that have assessed bleeding risk factors in MOS are few in number and quite heterogeneous. ASH is not aware of any studies in MOS that have specifically identified patients at high risk of VTE or bleeding and then assessed some modification of usual TP.	We have evaluated the characteristics which predict or differentiate risk if VTE and bleeding regardless of TP agent used recognizing that other factors aside from the surgery itself may alter risk of VTE and bleeding and should be considered in weighing the benefits and harms of TP. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. In the event where quantitative analysis is not possible for a KQ, qualitative analysis was completed. Additionally, we have used the future research needs to elaborate on such areas which have been identified as a result of the CER.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 3: ASH suggests increasing the clarity of the question and recommends the following: "Is asymptomatic DVT, assessed by routine contrast venography or DUS, a reasonable and appropriate surrogate outcome for "clinically-important VTE?" There are articles in the current literature to help answer this question .1,7	Thank you for this comment and for the references you provide. The importance of asymptomatic DVT is an area of controversy as is what constitutes a "clinically-significant VTE". That is evident even in the public reviewer's comments that we have received so far. We have chosen to include both symptomatic and asymptomatic DVT as the intermediate outcome evaluated as a CER must satisfy the needs of a variety of stakeholders including clinicians, patients, and policy decision makers.

Commentator & Affiliation	Section	Comment	Response
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 4: ASH believes this question is problematic for several reasons. First, there are no trials comparing one of the modalities of interest to no TP in the past 25 years. Furthermore, the data on antiplatelet agents is well-established. The 2008 ACCP guidelines gave a Grade 1A recommendation against aspirin as TP for any patient group and the 2010 UK NICE guidelines do not include aspirin as TP for any patient group.1,8 There are no injectable DTIs approved for TP, and there are no data looking at PTS after a specific modality of TP. There appears to be an association between wound bleeding and infection but there is no direct evidence linking any prophylaxis modality to wound infection. Finally, there are no useful data related to the following proposed outcomes in MOS: fatal PE, readmission, discomfort, all-cause mortality, re-operation, or fatal bleeding. Therefore, this question cannot be directly answered and the use of indirect comparisons is not acceptable.	Thank you for this comment. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. In the event where quantitative analysis is not possible for a KQ, qualitative analysis was completed. Additionally, we used the section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER. CERs have to satisfy the needs of a variety of stakeholders including clinicians, patients, and policy decision makers. As such, a more inclusive approach to selecting outcomes, such as the one we are proposing, will allow each stakeholder group to have the information that they need to make informed health choices. We agree that indirect comparison is insufficient to address this KQ and therefore we did not use of indirect comparisons.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 5: This is a clinically relevant question. Please refer to the numerous systematic reviews, meta-analyses and evidence-based guidelines that have addressed this question. 1,8	Thank you for your comment. We systematically identified similar meta-analysis conducted on this topic and present the findings in a summary table within the report. Additionally, we refer to the findings of these meta-analyses within the discussion of the report.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 6: Again, ASH considers this to be a potentially very important question but ASH is also aware that there are very few direct comparisons between agents within one class of TP modalities.	We agree that indirect comparison is insufficient to address this KQ and therefore we only included direct comparison trials. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. In the event where quantitative analysis is not possible for a KQ, we qualitatively analyzed data. Additionally, we used the section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER.

Commentator & Affiliation	Section	Comment	Response
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 7: Again, ASH considers this to be a potentially important question but is also aware that there are very few direct comparisons of combined vs. single modality TP and most of the listed outcomes have never been assessed in trials. Therefore, this question cannot be definitively answered.	Please see response to KQ 6. Also, in a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. In the event where quantitative analysis is not possible for a KQ, we qualitatively analyzed data. Additionally, we used the section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 8: ASH notes that the effects of post-discharge TP on both surrogate and clinically important outcomes have been reasonably well studied and there are multiple systematic reviews/meta-analyses on this subject.1,9 However, even in these trials, only asymptomatic DVT, symptomatic VTE and bleeding have been assessed. The other outcomes have not been assessed.	Thank you for this comment. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. In the event where quantitative analysis is not possible for a KQ, we qualitatively analyzed data. Additionally, we used the section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 9: ASH notes that there are no data on this issue. Not a single randomized trial has specifically addressed MOS patients with a contra-indication to antithrombotic agents. Furthermore, there is not a single RCT of the role of IVC filter use for any patient group as primary prophylaxis (with or without a contraindication to anticoagulant TP).	Thank you for this comment. In a CER, we are asked by AHRQ to pose the most important key questions whether or not they can be readily answered by the literature base. The absence of an endpoint in a CER should reflect its relative lack of importance and not a reflection of paucity of data. In the event where quantitative analysis is not possible for a KQ, we qualitatively analyzed data. Additionally, we used the section dedicated to future research needs to elaborate on such areas which have been identified as a result of the CER. A CER assesses the balance of benefits and harms, the strength of evidence, and applicability. Therefore, we present evidence of benefits and harms with accompanying strength of evidence ratings.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 10: ASH suggests that these patient populations be considered separately. The data are limited in these populations and ASH suggests that you refer to existing reviews of the literature.1	We definitely agree and have further specified the surgical populations in the key question and provided even more detail in the methods section of the protocol.

Commentator & Affiliation	Section	Comment	Response
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Key Question 11: ASH notes that there are inadequate data to be able to answer this question.	Thank you for this comment. Please see response in KQ 8.
Lawrence A. Solberg, Jr., MD, PhD Chair, Committee on Practice, American Society of Hematology	Methods	Additional Comment: Throughout the AHRQ questions, the term "immune-mediated thrombocytopenia" is used. ASH suggests that the correct terminology is "heparin-induced thrombocytopenia".	Thank you for this comment. We have changed the term "immune-mediated thrombocytopenia" to "heparin-induced thrombocytopenia". We wanted to specify that we were not evaluating the early phase mild thrombocytopenia due to heparin therapy through a non immune mediated phenomenon.
Peter Wildgoose, Ph.D. Cardio-vascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	Dear AHRQ VTE Report Generation Team: Thank you for the opportunity to comment on the key questions for the proposed comparative effectiveness of VTE prophylaxis in orthopedic surgery report. After reviewing the content of the questions, including the background information, we are forwarding our comments via this correspondence. A number of comments are global in thought, and some relate to specific questions or the background information/figure. Comments are titled by issue of consideration. GLOBAL - Bleeding Outcomes: Due to variation in major bleeding criteria across clinical organizations and drug studies, suggest that a standard definition be included in the question, possibly the ISTH definition. Consider removing the "minor" bleeding category and list out the individual components instead. The individual components of "minor" bleeding could include all events that do not fit the "major" criteria such as gingival bleeding, excessive wound hematoma, nose bleeding and others. If consensus on definitions of "major" and "minor" cannot be reached, it may be clearer to individually list the bleeding events because a consistent definition does not exist.	We agree that the definition of bleeding reported in the literature is not standardized and likely varies between studies. As such, we have recorded the definitions for major and minor bleeding used in each trial and presented them in the evidence tables.

Commentator & Affiliation	Section	Comment	Response
Peter Wildgoose, Ph.D. Cardio-vascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	GLOBAL - Inclusion of Additional Safety endpoints: To evaluate the complete individual product safety profile, it is suggested to include question(s) on other safety endpoints (ex. gastrointestinal effects, renal effects, etc.) in addition to bleeding outcomes. One adverse event of particular interest following any surgery is wound complications such as surgical-site bleeding, oozing etc. Additional questions on the effect of VTE prevention therapies on wound complications are suggested.	Thank you for this comment. Although raised to the TEP, these outcomes were not added to the protocol and therefore not evaluated in this CER.
Peter Wildgoose, Ph.D. Cardio-vascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	GLOBAL - Dose timing: Dose timing following surgery is an important factor in safety and efficacy endpoints although the actual timing varies across the clinical trials of the anticoagulant classes. Therefore, including an additional question or subset analysis regarding the optimal benefit/risk timing of the first dose after surgery can shed additional clarity on the observed safety and efficacy endpoints.	Thank you for this comment. However, the research question regarding the timing of prophylaxis relative to surgery was not defined in the protocol and is beyond the scope of the CER at this time.
Peter Wildgoose, Ph.D. Cardio-vascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	GLOBAL - Net Clinical Benefit: Inclusion of questions around the NCB can provide the balance of adverse effects of anticoagulation with the benefit of VTE reduction. With clearly defined methodology, the net clinical benefit of VTE prevention therapies can be weighed against its risks.	Thank you for this comment. CERs do not include an economic evaluation and therefore the NCB was not evaluated.

Commentator & Affiliation	Section	Comment	Response
Peter Wildgoose, Ph.D. Cardiovascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	GLOBAL - Fig 1 Draft Analytic framework for VTE prophylaxis: The framework of VTE prevention in orthopedic surgery provided in the diagram may not adequately capture actual clinical practice algorithms. First, we suggest that the framework begin with a risk assessment of patients undergoing orthopedic surgery for VTE risk and bleeding risk based on individual parameters such as age, renal, hepatic function, and prior VTE/bleed events. Secondly, the direct association in this diagram of "Thromboprophylaxis" and "Adverse Effects of Treatment" may not provide a complete picture of the effect of anticoagulation and other treatments. Additionally, the adverse effects listed are multivariate and dependent on additional factors. Inclusion of adequate risk assessments can minimize adverse effects. Lastly, further clarification is needed on how DVT (asymptomatic or symptomatic, proximal or distal) is considered an "Intermediate" outcome versus a "Final health outcome".	Thank you for this comment. The analytic framework is not intended to reflect actual clinical practice algorithms. Instead, the analytic framework reflects a logic chain linking the population of interest with the interventions and outcomes (intermediate, safety and final health) and how each key question helps to address these links. Key question 2, which addresses the characteristics which may alter the risk of VTE and bleeding, is considered in all three pathways which link the population to outcomes (intermediate, safety, and final health outcomes) of interest. The importance of asymptomatic DVT is an area of controversy. While it may increase the risk of PE and post-thrombotic syndrome, asymptomatic DVT would still be considered an intermediate outcome in the analytic framework linked to these other final health outcomes. In the evaluation of key questions 4-11, we have included both DVT and PE outcomes. We have chosen this more inclusive approach so that stakeholder groups (i.e. policy decision makers, clinicians, patients) have the information that they need to make informed health choices.
Peter Wildgoose, Ph.D. Cardiovascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	GLOBAL - Special Populations: Following an adequate risk assessment of patients undergoing orthopedic surgery that evaluates co-morbid conditions and other patient factors, it is important to evaluate the effect of anticoagulation therapy in special populations such as elderly, renal, hepatic status, etc. An additional question or subset analysis based on these special populations should be considered.	Thank you for this comment. The evaluation of special populations such as those suggested in your comment (i.e elderly, renal or hepatic status) is beyond the scope of this CER.

Commentator & Affiliation	Section	Comment	Response
Peter Wildgoose, Ph.D. Cardiovascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	GEN - Table 1: The following is suggested to add clarity and accurately categorize new agents: Include separate column for indication of investigational versus FDA-approved compounds. Currently, the distinction is not apparent. Move dabigatran to a separate "Direct Thrombin Inhibitor" category to reflect its mechanism of action versus Direct Factor Xa Inhibitors: rivaroxaban and apixaban. Move fondaparinux to a separate "Indirect Factor Xa Inhibitor" category to differentiate from the Direct Factor Xa Inhibitors, rivaroxaban and apixaban.	Thank you for this comment although a table as described in the comment is not in the CER,
Peter Wildgoose, Ph.D. Cardiovascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	Q6 - Expanding Drugs Evaluated: Requesting expansion of drug classes to be included in this question's evaluation as only two classes of therapies are listed: LMWH and mechanical devices. Other classes mentioned in Question 5 should be incorporated in the review parameters for Question 6.	Thank you for this comment. The TEP did not feel that directly comparing one agent to another from the same class other than LMWH and mechanical devices would be as important to healthcare decision makers as comparing LMWHs to each other and mechanical devices to each other.
Peter Wildgoose, Ph.D. Cardiovascular Therapeutic Area Lead Ortho-McNeil Janssen Scientific Affairs Payal Desai, Pharm.D. Associate Director Ortho-McNeil Janssen Scientific Affairs	Methods	Q5/6 - Ex US Experience: For non-FDA approved (US-investigational) products that are available in countries outside of the US, inclusion of questions regarding any ex-US utilization could provide real-life product experience data. Again, thank you for the opportunity to submit our comments. Should any clarification be required on the above, we would be available for discussion.	Thank you for this comment. In a general CER includes only products with a current FDA approval for an indication. Therefore, we cannot expand the evaluated products to include those not yet approved or those previously approved, since they are not currently available.