Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Primary Care Management of Abnormal Uterine Bleeding*

Draft review available for public comment from July 11, 2011 to August 9, 2012.

Research Review Citation: Hartmann KE, Jerome RN, Lindegren ML, Potter SA, Shields TC, Surawicz TS, Andrews JC. Primary Care Management of Abnormal Uterine Bleeding. Comparative Effectiveness Review No. 96. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 13-EHC025-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2013. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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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.

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Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Executive Summary ES-11 l. 55-56	The sentence beginning 'The treatment effect was large..." is unclear.	We have added the quantitative data.
Peer reviewer #4	Executive Summary ES-11 l. 56 p.82 l.32	I believe the authors mean 'predominantly', not predominately'.	We have revised to "predominantly".
Peer reviewer #4	Executive Summary Tables B and C	Tables B and C are difficult to interpret without information on what the comparator group(s) were	The strength of evidence tables are standard tables that report the assessment of risk of bias and other domains across the body of evidence for a particular outcome. These tables are not intended to provide global summary judgments of the relative benefits and harms of treatment comparisons.
Peer reviewer #4	Executive Summary	What does 'Direct' really mean in Tables B and C, where it represents directness of the evidence that treatment improves the symptom?	Direct means that evidence links the intervention directly to improvement in the health outcome of interest in this review.
Peer reviewer #5	Executive Summary ES-1 l.15	Add Munro reference to these "norms"	As the data in the paper by Munro 2012 does not include any additional data on norms, we have not added the reference. See comment below. We understand the challenges to the definition of "normal" as Munro clearly outlines in the paper.
Peer reviewer #5	Executive Summary ES-1 l.54	Add coagulation defects	We have Inserted in text: "…the cervix or uterus, coagulation defects, and systemic disease."
Peer reviewer #5	Executive Summary ES-5 l.42	What progestogens (not all were included in this study) so not all should be suggested.	We have identified specific progestogens when referring to individual studies.
Peer reviewer #5	Executive Summary ES-5 l. 50,52	Define or restate – infrequent not "irregular" uterine bleeding.	We have clarified that irregular can be frequent or infrequent.
Peer reviewer #5	Executive Summary ES-7 l.50-51	A much better study is available the Hurskainen found that 52% of women in the LNG IUS group avoided hysterotomy. [Hurskainen R, et al. *Lancet*. 2001;357(9252):273-7]	This study, a RCT of LNG-IUS versus hysterectomy, did not qualify for inclusion in our review.
Peer reviewer #5	Executive Summary ES-8 l. 6	These studies do not demonstrate the superiority of NSAIDs to all progestin-only oral norethisterone given during the luteal phase was tested. To generalize to all progestogen therapy is misleading.	We changed the wording to "NSAIDs are similar in effectiveness or superior to oral norethisterone.
Peer reviewer #5	Executive Summary ES-8 l.13	Really what was seen was no differences in reduction in MBI (no differences in MBI).	We have changed wording to "no differences in MBL reductions…"
Peer reviewer #5	Executive Summary ES-8 l. 13	The trials with COCs showed reduction of 43-68% is clearly better than 20-59%. Why mention Progestasert?	A small crossover trial that compared NSAID to low dose COC did not show superiority of COC. We deleted the reference to Progestasert.

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Peer reviewer #5	Executive Summary ES-9 (8?) l. 26-28	Which progestogens? Need a reference for the sentence study "In compared to. . ."	We added text to clarify the progestogens. "…comparison to two progestogens (northisterone and medroxyprogesterone acetate), COCs, and…"
Peer reviewer #5	Executive Summary ES-8 l.34	Reduction in bleeding for women with HMB was 76%	The Fraser 2011 paper reports mean reduction in MBL of 69%, the Jensen 2011 paper reports 64.2%
Peer reviewer #5	Executive Summary ES-8 l. 39	Need to give range of effectiveness in CDC comparator arms	The strength of evidence tables provide the range of effectiveness for interventions from fair and good quality studies that reported reductions in MBL.
Peer reviewer #5	Executive Summary ES-10 l.4	Why mention dydrogesterone? Not available in US.	We have deleted the reference to dydrogesterone in the discussion on harms but have retained it when referencing specific studies for which it was a comparator.
Peer reviewer #5	Executive Summary ES-10 l.6	Why mention risks of DMPA when you did not cite D<PA as a possible treatment? There are several other studies that have looked for fracture risk and have not found any.	DMPA was used as a comparison treatment in included studies.
Peer reviewer #5	Executive Summary ES-10	Which progestogens? Not progestin-only pills or cyclic MPA or NETA.	We have indicated specific progestogens when referring to individual papers.
Peer reviewer #5	Executive Summary ES-10 l.17	Why restrict to oral contraceptives – the same risk prevalence to vaginal rings.	The executive summary includes the summary of LNG-IUS and vaginal ring.
Peer reviewer #5	Executive Summary ES-10 l.19	Placebo controlled studies have failed to find any increase in the rate "more common side effects." Need to delete those comments.	We have deleted "more common"
Peer reviewer #5	Executive Summary ES-10 l.22	Might mention how very rare the serious risks.	We have mentioned this.
Peer reviewer #5	Executive Summary ES-10 l. 26	Cigarette smoking is not a contraindication to COC use in the US for women ≤ 35 years. Age over 35 is not a contraindication to COC use.	We have changed text to"… contraindications which include cigarette smoking in women over age 35…
Peer reviewer #5	Executive Summary ES-11 l. 5	Why not quote numbers – "not race" is not helpful.	We have changed text to" noting that expulsion occurs 6-16% of the time" Package insert data is reported as 4.9% in the full report but that is not one of the 3 references for this sentence
Peer reviewer #5	Executive Summary ES-11 l. 10	Are we sure the lightheaded, dizziness was not due to heavy bleeds?	This was not possible to determine
Peer reviewer #5	Executive Summary ES-12	Table needs to be more specific –luteal phase progestin's not "progestogen"	We have added table notes to indicate the specific comparators.
Peer reviewer #5	Executive Summary ES-12 l. 47	Why wait to end of this section to report additional benefits.	We have deleted the statement on additional benefits. We agree it was misplaced.

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Peer reviewer #5	Executive Summary Es-13 l. 53	Mention coagulopathy explicitly. Very good, but there are trials of LNG/IUS in women with coagulopathy.	The evaluation of LNG IUS in women with coagulopathy was outside scope of this review.
Peer reviewer #5	Executive Summary ES 14, l. 3	Should not use PDA labelling or reports of drug-drug interactions, but use US MEC instead.	We are not using the U.S. Medical Eligibility Criteria for Contraceptive Use, 201 from CDC MMWR as a source for harms data. We relied on Package Inserts as the standard source of regulatory data on harms for the included interventions.
Peer reviewer #5	Executive Summary	Any information that cabergoline is helpful in women with PCOS?	Some studies have suggested a possible mechanism of action for Cabergoline / Bromocriptine (dopamine agonists) to improve cycle regularity. See: Paoletti AM, Cagnacci A, Depau GF, et al. The chronic administration of cabergoline normalizes androgen secretion and improves menstrual cyclicity in women with polycystic ovary syndrome. Fertil Steril. 1996 Oct;66(4):527-32. PMID: 8816612. The text in the main report, in the Medical Therapies for KQ1A addresses this question noting, "Mechanism of effectiveness for restoring cycles in PCOS may include amplifying dopamine neurotransmitter actions in the central nervous system resulting in hypoprolactinemia and lower levels of hormone signals that increase androgen production by the ovary.[55]"

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Peer reviewer #5	Executive Summary ES-15, l. 4	Cyclic progestin also provides a non-contraceptive treatment option.	The search did not identify randomized clinical trials of cyclic progestins of fair or good quality that compare cyclic progestin to placebo. Vaginally compared to orally administered progesterone on a cyclic schedule was associated with similar improvements across groups. However this single trial was small and of poor quality, providing overall insufficient evidence. In other trials of direct comparisons to other agents, progestogens were not superior to the agent under study whether continuously or cyclically administered. We have not revised the conclusions because the evidence is insufficient when applying EPC methods.
Peer reviewer #5	Executive Summary/General	I will continue to send you comments on the rest of the document as I develop them, but most of the comments I made in the Executive Summary percolate through the rest of the document.	Thank you.
Peer reviewer #7 (TEP	Executive Summary ES-1, l. 20	Include notion that question 2-20 not normal	These summary population norms are supported by the provided citations. Though these are the 5th and 95th percentile cut offs, it does not mean that some women would not present for care if their cycle regularity were to be this widely variable. This is why we note that symptoms outside of normal for the individual matter and deserve evaluation.
Peer reviewer #7 (TEP)	Executive Summary ES-1 l. 40	anovulatory doesn't mean ovulatory disorders	We have edited the text for clarity. "…for the treatment of both irregular and abnormal cyclic menstrual bleeding"
Peer reviewer #7 (TEP)	Executive Summary ES-2 l. 8 P 33 L 24	evaluate for not rule out	We have edited the text for clarity to, "The relevant population for this review includes nonpregnant women from menarche to menopause who have had AUB for three months or longer, that is not attributed to structural abnormalities, systemic illnesses, or medications."

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #7 (TEP)	Executive Summary ES-3, l. 38	Many TA RCTs before 1980	Our review only included studies published in 1980 or later. During topic refinement we decided to restrict the search to studies from 1980 forward in order to assure literature is relevant to current secular trends in practice as well as available treatment strategies.
Peer reviewer #7 (TEP)	Executive Summary ES-7 l. 24 and l.40	Inconsistency in terminology - abnormal cyclic and HMB	We changed heavy menstrual bleeding to "abnormal cyclic uterine bleeding"
Peer reviewer #7 (TEP)	Executive Summary ES-7 l. 51	check reference 37...patients may have been scheduled for hysterectomy	The sentence has been changed to " A single study among women scheduled for hysterectomy found that LNG-IUS users were more likely to cancel their surgery compared to women in the usual care group."
Peer reviewer #7 (TEP)	Executive Summary ES-8 l. 6 and l. 13	progestin can't be naked...have to specify local or systemic and systemic as oral or parenteral, cyclic or non cyclic	We changed the text to specify "oral norethisterone"
Peer reviewer #7 (TEP)	Executive Summary ES-9 l. 18	abnormal irregular bleeding?	We changed the wording to irregular uterine bleeding
Peer reviewer #7 (TEP)	Executive Summary ES-9 l. 40	Heading Progestin not progesterone	We feel the term progestogen is the broader more inclusive term of the variety of agents that would have been eligible for review and were identified for review. From a US medical reference, the first definition of progestogen is "Any agent capable of producing biologic effects similar to those of progesterone; most progestogens are steroids like the natural hormones." The first definition for progestin is "A hormone of the corpus luteum."
Peer reviewer #7 (TEP)	Executive Summary ES-10	Concern re progestins and thromboembolic disease and how this is interpreted and represented	We have reported that "Some data suggest use of progestogens is associated with increased risk of deep venous thrombosis," and removed the word "intriguing" with respect to the suggestions based on the Sundstrom paper. The suggestion that increased risk of thrombosis may be an example of confounding by indication is further discussed in the Future Research Needs section of the main report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	Needs discussion of terminology. See Woolcock 2008; Fraser and Critchley 2007; Munro and Critchley 2011	A description of terminology along with references to the noted citations is included in the Introduction of the main report.
Peer Reviewer #1	Introduction	Also need to discuss outcome assessment with alkaline hematin the gold standard	We have inserted a statement, "In the research setting, the alkaline hematin method is the preferred technique for direct measurement of total menstrual blood loss (MBL)."
Peer Reviewer #2	Introduction	Good summary, great overview.	Thank you for your comment.
Peer Reviewer #3	Introduction	The tables on page ES-2 and page 5 refer to "problem bleeding", but this term is never fully defined. In the executive summary, it is not defined at all. In the full report, it is addressed on page 1, but no definition is included and there does not seem to be a consensus in the existing literature. One aspect of this problem could be addressed by recognizing the limited and almost nonexistent evidence on patient preferences in the papers reviewed. This could be included in the research needs section, but also should be addressed as a limitation.	One page 1 of the Introduction we discuss problem bleeding and provide descriptions of specific types of problems. We concur the literature is highly varied in the operational definitions of bleeding that are used by research teams. In describing the studies we are careful to provide inclusion and exclusion criteria in evidence tables and to discuss applicability. We have added patient preference research as a need in the context of future research and we have added additional information summarizing where possible whether participants assessed their bleeding as improved as a result of interventions.

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Peer Reviewer #3	Introduction	The definition of this as about primary care seems forced. A cross national comparison of care systems is glossed over in one sentence. There is no discussion of the fact that primary care and referral care patterns vary dramatically by access and care system variations unrelated to care setting. The exclusion of referral patient studies similarly seems clinican-based, when the appropriate focus of this kind of comparative effectiveness evidence review is on the PATIENT centered aspects of care for bleeding. This problem is present throughout the writing, but is particularly an issue with the Applicability sections. There simply is no data presented on the actual type of care and whether primary care, comanaged primary Medicine and Gyn care, or primary care referral to primary Gyn care was being delivered in these studies. Thus some of the referral care data that was excluded might be most appropriately included if the goal is to understand comparative effectiveness from the patients perspective. The exec summary has this problem, as does the writing on page 73-85 in the discussion section of the review. A particular example is ph 77 on progesterone, where primary care is related to "standard care", whatever that is.	This review is focused on the evidence available to inform selection of nonsurgical options to treat AUB with an emphasis on interventions that are accessible to and within the scope of usual practice for primary care practitioners in a clinical care setting in the United States. This means that while we *did not* restrict literature review to studies conducted only in primary care settings, we did restrict the review to include only those interventions that could be deployed in primary care. [We have expanded this information in the methods section and include both sentences above.] Patterns of care and referral/co-management are not the topic of this review rather we hope to estimate effectiveness of interventions appropriate for patients in primary care settings. Lastly, we have dropped the word "standard" noting the formulations are used in care in the United States.
Peer reviewer #4	Introduction	The introduction outlines the importance and prevalence of the problem and the common treatments in current practice. They outline their analysis strategies for this CER and provide satisfactory detail about their approach and methods.	Thank you.
Peer Reviewer #6	Introduction	On page 1 the definition of AUB does not agree with the FIGO PALM-COEIN classification (see Int J Gynaecol Obstet 2011;113:3–13).	The introduction now includes a discussion of the relatively recent introduction (2011) of the FIGO classification and the fact that the existing literature does not map directly to the new system.
Peer Reviewer #6	Introduction	AUB is NOT a diagnosis of exclusion. Instead it is a broad category within which there are subgroups according to etiology. For example, "AUB-L" refers to AUB caused by leiomyomata, a structural cause and "AUB-O" refers to AUB caused by ovulatory dysfunction.	We have deleted the statement about "diagnosis of exclusion" and we now explain what categories of the PALM-COEIN subgroups the CER is designed to address.

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Peer Reviewer #6	Introduction – AF	The Analytic Framework in Figure 1 also refers to excluding several causes of AUB. Which subtypes of PALM-COEIN remain and are the subject of this review?	The text now explains the portion of PALM-COEIN addressed by the CER but emphasizes that for methods we are not reviewing literature focused on the excluded conditions. The existing literature does not readily map to the new classifications in terms of applying operational definitions that specifically define populations of women with AUB-O, AUB-E, or AUB-N. Nonetheless, these are the conditions most likely to result in the symptom profile for which this review was designed: problematic irregular or abnormal cyclic bleeding.
Peer Reviewer #7 (TEP)	Introduction p. 1 l.25	typo 2 not wo	This has been corrected.
Peer Reviewer #7 (TEP)	Introduction p. 1 l.45	AUB is NOT a diagnosis	We have removed the related sentence.
Peer Reviewer #7 (TEP)	Introduction p. 2 l.53	progestin no progesterone	Progesterone-releasing is the correct term from the product materials.
Peer Reviewer #7 (TEP)	Introduction p. 3 l. 6-11	Requires a rewrite	The materials about professional society recommendations are current and additional literature references have been added to describe contemporary practice.
Peer Reviewer #7 (TEP)	Introduction p. 3 l.15	Strike prospective	We have deleted the word “prospective”.
Peer Reviewer #7 (TEP)	Introduction p. 3 l.17	progestin not progesterone	The IUD is “progesterone” releasing.
Peer Reviewer #7 (TEP)	Introduction p. 3 l.25	treating AUB-E not AUB	This literature and most clinical guidance predates the term AUB-E. We have noted parenthetically that the newer term would be AUB-E.
Peer Reviewer #7 (TEP)	Introduction p. 3 l.27	wrong...the role of PGs is incorrect, and in insufficient detail.	We have edited our text in line to provide greater detail and improve consistency with content of the cited references.

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Peer Reviewer #7 (TEP)	Introduction p. 3 l.45	Menorrhagia	We have edited to remove the clinical term and replaced with “heavy menstrual bleeding.”
Peer Reviewer #7 (TEP)	Introduction p. 3 l.49	what is thick growth? Confabulation.	COCs do induce relative endometrial atrophy (thinning). It does not seem to us to misrepresent the effect by stating that COCs discourage thick growth of the uterine lining.
Peer Reviewer #7 (TEP)	Introduction p. 4 l.8	additional data are needed	We have edited the text and included an additional citation.
Peer Reviewer #7 (TEP)	Introduction p. 4 l.13-14 l. 23	This is too simplistic a description of the physiology and role of progesterone for this scale of project. Line 23 “encourage endometrial quiescence” and “prevent growth” are the type of description I would expect for an educated lay audience.	We appreciate this comment and we have made additions and edits to the text to provide additional detail regarding the potential physiologic effects of this therapy in women with AUB.
Peer Reviewer #7 (TEP)	Introduction p. 4 l.16-17 and l.19	It would be better if it read “administration of progestins are intended…)	This has been corrected to read progestogens which are the broader classification of drugs in this category and we are purposefully using this term to incorporate the whole class of compounds. See the comment above in the section for the Executive Summary for definitions of progestins and progestogens.
Peer Reviewer #7 (TEP)	Introduction p. 4 l.25	American College of Obstetricians and Gynecologists not what is there	We reviewed both ACOG statements cited and confirmed that this sentence is in line with their recommendations?
Peer Reviewer #7 (TEP)	Introduction p. 4 l.26-27	(noncontraceptive used ?)	We have corrected to “noncontraceptive uses”.
Peer Reviewer #7 (TEP)	Introduction p. 5 l.38	I find the term “oral hormone treatments” uninformed. There are at least scores of “hormones”. We are speaking specifically about gonadal steroids.	For brevity and simplicity we prefer oral hormone treatments. Given that these medications are to be used for AUB it seems clear in this context.
Peer Reviewer #1	Methods	Methods: given the imprecision in terminology, these are fine	Thank you.

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Peer Reviewer #1	Methods	see Fraser 2011 or Jensen 2011 for a better classification of symptoms that might be managed.	The description of the subtypes of AUB and of management strategies was developed with our Technical Expert Panel. This substantively shaped the review; revision to encompass a new definition or to revise is not possible after the completion of a review. We concur that the operational definitions applied in both the Fraser and the Jensen papers are clear and readily replicated. In this way they could serve as strong examples of the improvements needed in the overall literature. These sister studies, which appear to be the same protocol used in a US and European multisite RCT, were both scored as good quality trials and included in the review.
Peer Reviewer #2	Methods	methods included an in depth analysis of literature exclusion of reports and why was clear inclusion of reports was clear	Thank you.
Peer Reviewer #3	Methods	See other section comments.	This has been noted.
Peer reviewer #4	Methods	Yes, the inclusion and exclusion criteria are carefully described and justified. The search strategies are comprehensive and explicitly stated. Outcome measures in studies of uterine bleeding are especially problematic and rather unsatisfactory. For example to measure amount of monthly bleeding, one approach is to collect sanitary materials and quantify amounts through laboratory analysis such as the alkaline hematin method. Another approach is to use patient report of amount comparing with a standardized chart of some kind. Thus comparisons across studies are difficult. Statistical methods consist almost entirely of assessment of appropriateness of the methods used in the individual studies. Meta-analysis is not feasible. The authors did use a standardized measure of study bias.	We concur and have included discussion of these in several sections of the report.
Peer Reviewer #7 (TEP)	Methods	The inclusion/exclusion criteria are appropriate. The search strategies are sound.	Thank you.
Peer Reviewer #7 (TEP)	Methods	The PICOTS table includes a list of study outcomes sought in the literature search.	This has been noted.

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Peer Reviewer #7 (TEP)	Methods	On page 12, the Data Synthesis section describes the range and inconsistency of outcome measures. The decision to perform a narrative synthesis instead of a statistical meta-analysis is justifiable.	This has been noted.
Peer Reviewer #1	Results	Results: evidence for LNG IUS is strong (see general comment #4 below)	See response below.
Peer Reviewer #1	Results	evidence suggests E2VDNG might be different than other pills (see general comment #4 below)	See response below.
Peer Reviewer #2	Results	The results were a summary in several sections of the findings of how to treatment abnormal bleeding. It was clear, concise, with a good summary	Thank you.
Peer Reviewer #3	Results	See comments above re primary care...And clarity usability comments.	Primary care constraints are addressed above. The comments on clarity and usability are addressed below.
Peer reviewer #4	Results	The results section provides a great deal of detail on the individual studies, enough to be useful clinically, and enough so that an interested clinician could determine which to pursue further by going to the original paper. In my view, the key messages are provided both in the text and in the summary tables. The figures, tables, and appendices are well designed and seem complete. I know of no additional references that should be included.	Thank you for your comments.
Peer reviewer #4	Results	I am particularly impressed with the organization, which allows the reader/clinician to peruse either an overview of the studies of all treatments for a particular condition, but also to identify the subset of studies of a particular treatment. Thus a particular treatment can be compared to all other treatments used as comparators in the studies. Results are also provided within outcome metrics. Very useful, once the organization is understood.	We appreciate your comments.
Peer reviewer #4	Results	The authors of this study have managed to organize the results of a number of studies with many different treatments, comparators, and outcome measures, and to present them in several different formats such that a multitude of questions can be answered (as best as possible considering the limitations of some of the studies).	Thank you for your comments.

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Peer reviewer #4	Results	Identification of studies to answer Key Question 2 was especially difficult because harms are relatively rare and so many of the studies identified to answer KQ1 are small. It appears that the investigators were as meticulous in answering this question as for the questions assessing effectiveness of treatments. They have summarized major findings and then provided a detailed analysis of each treatment. It appears to be well and carefully done.	Thank you.
Peer reviewer #4	Results p.21 (or 52) l.3 Table 4	Four studies are alluded to, but Table 4 has only two studies.	The sentence mistakenly refers to the wrong table. This has been corrected and we have added an additional heading to separate the discussion of the two studies on dysfunctional uterine bleeding (Table 4) and the four studies of PCOS (Table 5).
Peer reviewer #4	Results p.23 (or 54) l. 54-55	What is meant by 'the research team restricted the population of women with PCOS who were eligible for inclusion.' In what way were they restricted?	This statement has been corrected. The original statement was an error.
Peer reviewer #4	Results p.25 l.33-34	How is, for example, a 121% increase in cycle regularity established? What is the metric?	Attempted to explain this unusual metric better by providing more detail.
Peer reviewer #4	Results p.71 l. 13	and extra 'women'	This has been corrected.
Peer reviewer #4	Results p. 78 l.45	'tow' should be 'two'	This has been corrected.
Peer Reviewer #6	Results	The study characteristics are clearly described in the narrative, figures, tables and appendices. The Key Points sections are clear and explicit and their messages are applicable.	Thank you for your comments.
Peer Reviewer #6	Results	The Search was executed through March 2012. Depending on the lag time to publication it may be warranted to search for more recent publications	We have updated the text, the counts, the diagrams, the figures, the tables, and appendices to include three additional studies for KQ1 and four papers for KQ2 that were identified in an updated literature search conducted in June 2012.
Peer Reviewer #7 (TEP)	Results p. 20 l. 26	Oral and vaginal progestins, not progesterone.	Thank you. We have revised the statement to "Both oral dydrogesterone and vaginal micronized progesterone gel administered on a cyclic schedule had comparable influence on normalizing timing of menses."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7 (TEP)	Results p. 21 l. 15	It is not clear what group of patients were being studies in Davis et al. Consequently one cannot assume that this is a pure AUB-O population. AUB-E wasn't acknowledged and patients were not systematically evaluated for AUB-C.	The 2000 study by Davis and colleagues included women who had "…at least a 2-month history of metrorrhagic, menometrorrhagic, oligomenorrheic,or polymenorrheic DUB…" Dysfunctional uterine bleeding was defined by the authors as bleeding with no organic cause and not attributable to systemic disease or structural pathology. We concur that one cannot conclude that the population is comprised exclusively of individuals with one or another specific type of AUB as defined by one of the nine subtypes outlined in the comprehensive and excellent 2011 PALM-COEIN classification system. Based on preliminary review of the literature and discussions with key informants, we elected to group and evaluate data from the published primary literature as either irregular uterine bleeding or heavy menstrual bleeding because these discriminations were the most apparent. We have clarified the first key point in Table 4 to indicate that the data from this study are based upon results from participants with AUB of mixed etiology. We have also edited the results section text for this particular study to indicate: "The study enrolled participants with a variety of menstrual concerns including heavy periods, frequent periods, irregular and heavy periods, and rare episodes of bleeding. Investigators did not systematically evaluate for the presence of disorders of hemostasis. The data is provided in aggregate for all participants regardless of their bleeding pattern or primary symptom. "

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Peer Reviewer #7 (TEP)	Results p. 21 l. 39	Reference 47 is not accurately described. Progestins were used in this RCT, one arm was vaginal progesterone while the other was an oral synthetic progestin. This description represents that oral progesterone was compared to vaginal progesterone either cyclically or on alternate days in a simulated luteal phase. Of course the title of the section "Progesterone Administration" which is incorrect is also revealing.	We have clarified the text as follows: "A single RCT sought to compare the efficacy of oral dydrogesterone, 10 mg twice daily for 10 days starting on cycle day 15, compared to vaginal micronized progesterone applied every other evening from cycle days 17-27." We have deleted "Administration" from the heading.
Peer Reviewer #7 (TEP)	Results p. 26 l. 25	There is a RCT from Scandanavia comparing LNG-IUS with hysterectomy with 5+ year followup. This may not have been captured, but it is RCT with followup beyond a year.	The Scandinavian trial in essence has no comparison group at five years to determine what the expected outcomes would have been with use of another strategy (i.e. it lacks a counter-factual comparison group), for this reason trials with a medication vs. surgical arms were not included in this review because they don't provide adequate comparators. We have modified the summary to indicate there are no "controlled" longer term follow-up studies.
Peer Reviewer #7 (TEP)	Results p. 26 l. 44-45	Idiopathic menorrhagia is not a FIGO term.	Noted
Peer Reviewer #7 (TEP)	Results p. 29 l. 6	Here is an example of lack of attention to detail. The Kaunitz study (57) is RCT using "luteal phase" or cyclic MPA. This is not specified in this manuscript.	We clarified that " MPA administered during the luteal phase of the cycle"
Peer Reviewer #7 (TEP)	Results p. 34 l. 49	"..progesterone-releasing intrauterine systems including the LNG-IUS". Another example….	The Cameron paper describes the progestasert as a progesterone releasing coil.
Peer Reviewer #7 (TEP)	Results p. 54 l. 49	I think that this statement misrepresents progestins. First of all, the qualifier regarding venous thrombosis risk of progestins being increased when estrogens are added doesn't belong here. It may be reasonable to state (somewhere) that it is frequently difficult to evaluate the impact of progestins because they are often administered in combination with an estrogen. I don't think that this work adequately evaluates the different progestins and why there may be differences in VTE risk.	We have removed comments about DVT risk. The literature update now includes one additional surveillance study of progestogen only methods that finds both thrombotic stroke and MI are more common among women using these methods than not. However it does not rise to the level of a key point statement.
Peer Reviewer #7 (TEP)	Results p. 60 l. 6	Syntax	We have revised the wording to read "Most of the studies reviewed were small and did not systematically compare adverse events across intervention groups".

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/ Conclusion	See above, this is weak and unfocused and leads to the impression that treatments are not as good as they are.	The discussion follows conventional structure for reporting of CERs which includes: State of Literature, Applicability, Strength of Evidence, Future Research Needs and Implications. This structure does lead to repetition of some concepts and materials. As to whether the report undervalues treatments, this report is unusual in the women's health context in that the majority of the interventions for abnormal cyclic bleeding are found to have moderate to high strength of evidence. This is an endorsement of the effectiveness of these interventions not an indictment. Nonetheless, the findings must be couched in the overall context of the quality of literature and what remains to be done.
Peer Reviewer #2	Discussion/ Conclusion	Discussion gave a good overview and summary	Thank you.
Peer Reviewer #3	Discussion/Conclusion	The description of research as "intriguing" should be resisted. While the review cited does raise important questions about the potential for confounding due to the association between heavy bleeding and thrombosis, this should be presented in a straightforward manner, and this issue should find its way to the research needs section of the review.	We have added the suggested research on potential for bleeding abnormalities among women with AUB to the future research needs summary.
Peer Reviewer #3	Discussion/Conclusion	The limitation of the quality of some of the studies due to the reliance on patient reported or recorded outcomes is discussed in the full report, but not so much in the summary. If there are studies whose quality would be significantly impact , it might be helpful to note that alongside the table, or even to consider a footnote or table note that would indicate which of the studies were downgraded only because of this criteria.	We have added the following information to the Summary of the Strength of Evidence and Findings section: "The complete scoring is found in the Appendix J. For KQ1B, risk of bias associated with blinding of patients, personnel and outcome assessment was most likely to compromise overall assessment of study quality. For KQ1A, risk of bias associated with blinding of patients and personnel and incomplete outcome data was most likely to compromise overall study quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion/Conclusion	The limitations of the study on COCs notes age over 18 in the population on page 81 as a reason to be cautious about extrapolation to younger adolescents. However, the studies on decision-making should be examined with similar rigor. Older adolescents and young adults cognitive maturity undergoes changes through age 24-25 with regard to development of decision-making ability, and higher executive function. Whether or not these groups were included in the studies in this section should be specified.	Thank you for the comment. We have looked at the age of the participants in the decision aid studies. Two of three decision aid studies specified age as an inclusion criterion. One study (Vuorma et al., 2003) recruited women between the ages of 35-54 and a second study (Protheroe et al., 2007) included women aged 30-55. The third decision aid study (Kennedy et al. 2002) did not require that study participants meet a specific age criteria, but did report that the mean age for the participants was 40 ± 7 years. We have revised the text under decision aids to include the following statement: "Study populations included women older than 30 and 35 respectively in the two that reported, so findings do not generalize to younger women. None found benefit which may or may not reflect how similar approaches would be received in a U.S. health care context or across a broader age span of women."
Peer Reviewer #3	Discussion/Conclusion	Would include a discussion of the difficulty in defining what is problem bleeding in the Applicability section, too, on page ES14, and in the Research Gaps. Need to understand what is 'normal' since the prevalence of abnormal is relatively high...	Under the section for final comments on Applicability, we have revised the text to address: "Overall applicability of this literature to providing care was high. However, often women who are in trials do not reflect the full range of those with abnormal bleeding seen in primary care and, as we have noted, groupings of participants do not correspond directly to newer classifications of sub-types of AUB."
Peer Reviewer #4	Discussion/Conclusion	The implications of the major findings are clearly stated, as are the limitations of the included studies. The authors discussed not only the applicability of the findings summaries, but also possible limitations because study participants often do not represent the full population with the condition.	Thank you.
Peer Reviewer #4	Discussion/Conclusion	The limitations section as well as the Future Research section will be a valuable resource for those wishing to pursue further studies of treatment for these conditions.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/Conclusion p.84 l.52	'fair' should be replaced by 'fare'	This has been corrected.
Peer Reviewer #4	Discussion/Conclusion p.87 l.54	'associated'	This has been corrected.
Peer Reviewer #6	Discussion/Conclusion	The implications of major findings are clear and the limitations are enumerated.	Thank you for your comments.
Peer Reviewer #6	Discussion/Conclusion	The ongoing research section identifies 4 studies that may provide additional information on relative effectiveness and safety.	Noted.
Peer Reviewer #6	Discussion/Conclusion-Future Research Needs	Under "Future Research Needs" the first bullet under "Abnormal Cyclic Bleeding" calls for more studies on the natural history of heavy menstrual bleeding. Although I don't disagree with this recommendation, the report does not summarize the evidence on that question, so the recommendation overreaches the database of this review. The other recommendations seem more closely linked to the evidence review.	We added the following to explain why this bullet point is important to future research: "….in order to better understand the boundaries of what constitutes normal bleeding patterns and to document the trajectory of AUB. This would for instance, contribute data about what factors predict severity and whether a proportion of cases are self-limited."
Peer Reviewer #6	Discussion/Conclusion	The Conclusions should include a statement about the evidence supporting behavioral and CAM therapies, which were stated to be a focus of this review.	They are summarized with respect to their outcomes related to KQ1A.
Peer reviewer #7 (TEP)	Discussion p. 74 and p. 77 l. 6 and l 43	What is dysfunctional uterine bleeding? This was eliminated in the FIGO system.	We have revised the wording except when describing the results or details of a specific study that characterized the patient population using the term "dysfunctional uterine bleeding".
Peer Reviewer #1	General	This is a very comprehensive report. Abnormal uterine bleeding is complicated, and the nomenclature complicates the science and a comprehensive review. The lack of precision in definitions is a major weakness in this report. . This hampers the ability to compare the results of studies.	We appreciate your comments.
Peer Reviewer #1	General	Furthermore, the lack of discrimination between outcome assessment blurs the significance of studies. The rigor of outcome assessment is as critical as study power of allocation of treatment	We have separated the reporting of results for individual outcomes where previously combined (e.g., pictorial blood loss chart scores were extracted from the MBL volume and percent reduction sections and moved into a separate and distinct section).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	While there is some discussion about the magnitude of improvement, this is lost in the abstract and executive summary. It is of great importance to women whether treatments reduce bleeding or normalize it.	Few measures were reported consistently across studies. In order to provide summary statements that incorporate data from the maximal portion of the studies, we have reported percent change in bleeding from direct methods and visual assessment in the summaries, because they were most often used. The trials did not consistently report normalization of bleeding in order to present summary evidence in the abstract. We have added a statement to the results section indicating the number of studies that incorporated measures of "normalization" as judged by estimated amount of bleeding, or by patient perception of normalization or satisfaction with bleeding characteristics.
Peer Reviewer #1	General	These factors combine to make the report confusing and less useful, as the conclusion that the LNGIUS is supported by only a moderate level of evidence would potentially mislead primary care clinicians. Likewise, lumping E2V/DNG with other OCs neglects the data from 2 well-designed RCTs.	In the context of this CER, "moderate" strength of evidence should in no way be construed as an indictment - it is a supporting judgment that indicates one would expect the intervention to be effective. The two trials noted (Jensen et al., 2011 and Fraser et al., 2011) did, in fact, form the basis of our assessment that there is high strength of evidence supporting COC use to improve abnormal uterine bleeding.
Peer Reviewer #2	General	The report is meaningful. The audience is defined. The key questions are appropriate.	Thank you.
Peer Reviewer #3	General	The key questions, analytic framework, methods and reviews are well defined and seem appropriate. The writing is clear and concise. The review is methodologically consistent and appears complete, except for a few specific concerns which are focused on the question of ovulation and audience/care setting.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	The authors are to be commended for a careful and detailed analysis of a large number of studies assessing effectiveness and safety outcomes for treatment of AUB, a highly prevalent problem for women. They were able to reduce the total number of studies to a relatively few randomized clinical trials, many of which were of poor or fair quality. This is an important study that should be helpful to clinicians in making treatment decisions. Nevertheless the amount of excellent research being conducted to answer the key questions regarding the regularity and heaviness of uterine bleeding is disappointing. Furthermore the studies that have been conducted are sufficiently different in treatments, comparator groups, and especially outcome measurement, that quantitative pooling of results is impossible.	Acknowledged. We share your concerns and have attempted to convey in the FRN section.
Peer reviewer #5	General	I appreciate the opportunity to comment on this excellent draft for the AHRQ guidelines for "Primary Care Management of Abnormal Uterine Bleeding." These will be very important, so it is important that we insure that the most important topics are covered and that our conclusions are specific. I would like to make general comments that I think would benefit from editing to achieve our goals. I am sending you my comments first on the Executive Summary now so I will be sure to have them to you before the discussion.	Thank you.
Peer reviewer #5	General	Be very clear in the conclusions, categories and definitions. For example, throughout the text "progestogens' are dealt with inappropriately as a group. Clearly treatment is not more effective than DMPA or the LNG IUS and may not be more effective than POOPs. I f we mean luteal phase progestins or daily oral or vaginal progestins, that should be stated. In one section" progesterone" is discussed in a more limited fashion but elsewhere almost all progesterone are combined.	We have revised to be more specific in the use of the word progestogens. Since this is intro the comments are intended to provide context for why a category of drugs might be used for the condition, later we state that we searched for trials relevant to KQ1A&B and would have included any progestogen available in the US as an agent of interest. Then in results, we discuss specific formulations for which we did identify trials (or trial arms) and lastly we summarize for the class of agents the harms and SOE for specific groupings, like the IUD and other administration. This was not an active area of the research and ultimately progestogens contribute little to the report.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #5	General	Surveys emphasize the sad fact that many OB-GYNs rarely think of coagulation defects as a cause of heavy bleeding, and that of those who do think of that etiology, they think only of Von Willebrand's and do not think of the most common causes, including acquired platelet aggregation disorder's. Since these guidelines will hopefully have substantial impact. I think that it would be helpful if we add explicit mention of this problem and add references. I am quite certain that readers may not think of this condition when we exclude women who have "systemic disease." Please add "coagulation defects" prior to "systemic disease" in every section.	We have specified that this systematic review excludes AUB that is due to "Coagulation defects" throughout.
Peer reviewer #5	General	I am not clear that we have not clearly defined what we mean in KQIA and KQ2 for "irregular uterine bleeding." It would be helpful to say that we mean "infrequent bleeding" using FIGO classification. "Irregular uttering bleeding' can include women who have frequent bleeding and the therapies we recommend in this category do not treat frequent bleeding.	We did not restrict KQ1 to a pattern of infrequent bleeding. The intention was to identify all trials in women with irregular (aka unpredictable) bleeding. For instance had we identified studies of women with light spotting throughout the month, or close together scant cycles, we would have reviewed these treatment trials. This is the correct description of the method and is not adapted post-hoc to fit the content of the literature identified. For reasons now described in the introduction these terms do not map to the recent (2011) FIGO classification because the literature predates the classification system and cannot be accurately retro-fit into the FIGO categories.
Peer reviewer #5	General	Why mention treatments that are not available or no longer available in the US and have not prosect of becoming available. Dilutes relevance of the work for practitioners.	We have noted only when they are the comparator. It is an arm in a trial that is eligible and we wanted to assure that readers understand that though the drug is addressed in the review as a comparison arm it is not an agent available in the US for these reasons that appear unique to this formulation.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #5	General	Similarly, why mention names of methods that you did not evaluate the benefits (DMPA)?	Initially we chose not to feature progestogens as they were typically included as a comparator in head-to-head studies intending to demonstrate equivalence or superiority for one of the included interventions. We now indicate the outcomes from progestogens arms in the strength of evidence table and include harms and other data relevant to progestogens as a potential treatment option.
Peer reviewer #5	General	Why include information about treatment formulations not available in the US? Should only include the 2 US trials that had reductions or more of 38 and 39%. Initially the European formulation inflates the effectiveness.	They are included only in instances in which the formulation that is not available was a comparison arm in an included RCT.
Peer Reviewer #6	General	These elements are all well described in the report. However, the abstract does not address the quality of evidence on behavioral and CAM therapies.	We have revised the sentence on strength of evidence in the abstract to "Several common interventions (including behavioral and complementary and alternative medicine) lack sufficient evidence."
Peer Reviewer #6	General- Abstract	The Abstract should define "primary care management" to include medical, behavioral and CAM therapies and make a statement regarding the quality of evidence regarding behavioral and CAM therapies.	We have revised the Abstract objective to keep the emphasis on the condition in the first sentence and to describe intended setting and sorts of interventions in the second.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	General	First of all, the authors are to be commended for acknowledging that there are issues regarding nomenclature and classification that have been addressed by the FIGO nomenclature and PALM-COEIN systems. At the outset, they seem to state that they will utilize these systems, but that is basically the last we see as the manuscript is full of the “old world” of DUB, menorrhagia, idiopathic menorrhagia and all of the related issues. What they essentially state is that they will be evaluating medical management of AUB-E and AUB-O. This should be stated up front, and, I think, in the title, for certainly, they do not address the medical management of AUB-A, -L, -C and –I. There is no discussion addressing the possibility that AUB-E or O could be present in women with asymptomatic leiomyomas, adenomyosis or polyps. This is an issue that should be engaged, and is particularly concerning in the “Future Research Needs” section (Page 117, Line 26) Related to this is an overall inadequate attention to the issue of AUB-C andits detection and treatment. We have evidence from a systematic review and metaanalysis, that women with cyclic HMB (called menorrhagia, Shankar et al) can be found to have biochemical evidence of von Willebrand disease in 13% of the subjects. In their review of the studies, they should have seen that few of even otherwise high quality studies systematically looked for evidence of a coagulopathy.	During the topic refinement period, we discovered that key groups and publications have adequately identified the research challenges related to an historical absence of standard definitions and have reviewed the existing body or literature to extract and organize the diverse list of clinical outcomes associated with abnormal bleeding. Furthermore, the questions related to nomenclature are difficult to address within a systematic evidence review. We will expand upon the issues related to operational definitions for abnormal uterine bleeding within the discussion and note how these issues impact the CER.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7 (TEP)	General	This type of report should spend some time on pathogenesis – if it had, the product would have been better. This is not surprising, for I see a reference to a US-produced textbook, somewhat notorious for providing misleading information regarding the pathogenesis of AUB, and I don't see the primary research that has informed us of the normal and abnormal endometrial biology that provide some explanation for the cause and rationale for the treatment of AUB-E and AUB-O. For example, the rationale for the use of COX inhibitors is well described in the literature, but these authors have incompletely described the mechanism, and what is there is incorrect. How does this provide insight to the primary care practitioner?	The focus of the report is systematic identification of the literature about the effectiveness of the interventions for improving the outcomes of women with AUB. Orientation to the rationale for use of types of interventions is linked to basic mechanisms to clarify why some agents have come to be preferentially used for one group of patients rather than another. It is not within the scope of comparative effectiveness reviews to also review and present the content of the pathophysiology literature. Rather our goal is to assure the population, intervention, comparison groups, timing, and setting of the studies is sufficiently clear to present summary findings, strength of evidence, and allow women and providers to assess the applicability of that literature to the specific care situation.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7 (TEP)	General	The complexities of the mechanisms behind AUB-O are also not clearly delineated, reflecting an inadequate amount of understanding of the issues. Indeed there is evidence that women who have anovulatory bleeding may have relatively light flow, whereas, as Hale et al have showed, those with luteal out of phase cycles may have very heavy bleeding. Indeed women with luteal out of phase (LOOP) cycles are ovulating but undergoing folliculogenesis in the luteal phase, elevated levels of systematic estradiol, and associated heavy uterine bleeding. With a project of this size, I would like to see this addressed to help edify the population of practitioners.	We have not emphasized mechanisms because the included RCTs did not select participants based on such mechanistic distinctions, rather on symptom profile. Most often this was done without attention to documenting literal ovulatory or endometrial status and without documentation of the cycle hormone profile (as in Hale), working rather from timing of menses, self-reported symptoms, and bleeding measures. We have reviewed the Hale paper about AUB in the menopausal transition that suggests LOOP as a potential etiology for some abnormal bleeding patterns. Hale and colleagues are the second group, the first being a case report, to describe this phenomena in 20 to 30% of women as the near the menopausal transition. Thank you for the pointer. We have now included additional information in the future research needs section about the potential for advancing research by understanding such subtypes, and have also modified the related portion of the introduction to indicate the condition is likely more complex than appreciated.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7 (TEP)	General	There is frequent, incorrect use of terminology and descriptions around the role of progestins in physiology, pathology and, especially therapy. The word “progesterone” should be restricted to the description of the substance produced by the ovary from the corpus luteum following ovulation, and, therapeutically, when the actual molecule “progesterone” is used. The authors frequently fail to stratify oral interventions into those that are continuous and those that are administered cyclically. Indeed, there are two types of cyclic administration that are described – a “luteal phase” or short cycle where the progestin is administered for (typically) 10-14 days each calendar month, or in the presumed luteal phase, and a long cycle where the progestin is administered for 25 or so days each cycle or month. They also don’t address progestin dose or potency – there are massive differences in many of these studies.	Thank you for this comment. We have used the actual name of the drug when we are referring to a specific agent that is progesterone. To indicate the category of drugs we prefer the term progestogen to progestin, drawing on the following definitions to make that distinction. From a US medical reference, the first definition of progestogen is “Any agent capable of producing biologic effects similar to those of progesterone; most progestogens are steroids like the natural hormones.” The first definition for progestin is “A hormone of the corpus luteum.” We appreciate the notation to emphasize the pattern of drug administration. We have confirmed that this is noted each time that progestogens were an arm in an included trial. Of note, no included trials addressed the use of a progestogen, other that the progesterone-releasing IUD, as the “drug-of-choice” for treating AUB. In each case the progestogen was the inferior treatment arm or not statistically superior. For this reason we have not emphasized the role of progestogens in treating AUB.
Peer Reviewer #7 (TEP)	General	I believe that the investigators have captured the relevant clinical trials, excepting those that involve tranexamic acid published prior to 1980. This might be an oversight for there were several.	The inclusion criteria were established and described in the protocol for this review. The rationale for inclusion and exclusion criteria was documented and reviewed with Key Informants during the topic refinement period. The investigators elected to include studies published in or after 1980 to ensure that literature was relevant to current secular trends in practice as well as available treatment strategies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7 (TEP)	General	I am concerned about the repetition involved considering the abstracts, executive summaries, full text and description of "harm". It is probably justified, but perhaps formatting the project differently would help make it an ultimately more usable document.	We are working into a standard AHRQ template described in methods guidance using conventional approaches for synthesis of the data. It is at times repetitive but each layer has increasing depth. Harm is a term of art in such reports and refers to any negative psychological, physical, or health system consequence associated with the intervention being studied. We have been diligent to define the term and to use it consistently throughout.
Peer Reviewer #7 (TEP)	General	I should add, but understand, that the authors have missed the July 2012 ACOG Practice Bulletin endorsing the FIGO nomenclature and PALM-COEIN systems, that also provides a related approach to investigation for cause.	We have added discussion of the FIGO classification in the introduction and been more explicit about the fact that it followed the conduct of the research that is reviewed here. The operational definitions and groupings of patients employed in the extant research do not map cleaning to the PALM-COIEN classifications. Hopefully the classification will be a major impetus to resolved and unify classification in future research.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7 (TEP)	General	In summary, there is abundant work in this project that should serve as a foundation for a rewrite. However, I think that this document should be reconceived and rewritten in a way that addresses the issues stated above – otherwise, it just serves to prolong the confusion.	The authors and majority of the advising TEP recognize the desirability of unifying classification schemes like the FIGO criteria. However, our fate as reviewers is to summarize literature that pre-dated this system and has study populations that cannot be grouped with confidence into AUB-O, AUB-E, and AUB-N. Practitioners and other peer reviewers report they find face validity in the populations we describe as those of interest for Key Question 1a and 1b. They understand which groups of women are addressed and report they are able to understand and apply the information as synthesized for women with complaints of chronic irregular uterine bleeding (problem bleeding [frequent or infrequent] of 3 months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease) or abnormal cyclic uterine bleeding (Problem bleeding of 3 months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease).
Peer Reviewer #1	Clarity and Usability	Well organized, but deficient due to above	See response for General Comment, “These factors combine to make the report confusing and…”
Peer Reviewer #2	Clarity and Usability	The main points are well organized, the conclusions can be used to inform.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Clarity and Usability	On page 9 it is noted that the key questions and analytic frameworks were posted on line and received no comments. Is there any evidence that posting these is an appropriate method for obtaining the desired input from practitioners, researchers, or other stakeholders in the evidence review or guideline development process?	We have followed the established EPC methodology for engaging stakeholders that includes triage, topic refinement, and input from technical experts. Public posting of key questions is an integral part of the EPC methodology to ensure transparency and further engage the consumers, clinicians, policymakers, and other health care decisionmakers interested individuals. The EPC considers incorporating feedback in the final key questions when comments are submitted. The EPC considers public posting an opportunity for involvement of the whole range of stakeholders and a way to ensure the broadest possible relevancy of the research report.
Peer Reviewer #3	Clarity and Usability	On page 12 the authors states their intention to provide an impartial narrative. See earlier note about 'intriguing', and also consider a major revision in the paragraph on Implications on page 84. The second sentence in this section should be deleted. In the 2nd paragraph in this section, the conditions are characterized as 'embarrassing and costly'. Yet no evidence has been presents to support this claim. Similarly, although costs are certainly a factor in access and use of care, there is no data that helps us understand the following sentences about coverage decisions. A discussion of the evidence base for these policy implications would be helpful. Again, if this evidence does not exist, then there is an opportunity to bring these questions forward to the needed research section.	We have reduced use of modifiers when presenting results, including the term intriguing. However, in discussion sections we have appropriated more liberty when framing the issues for the reader. We feel it is helpful to point out limitations, inconsistencies, and intriguing findings. We have added references to support statements as appropriate and have also reworded to clarify our intent regarding the discussion of potential impact of cost on treatment decisions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Clarity and Usability	I am not sure that I fully understand the difference between harms and side effects. I ink that this point also relates back to the lack of patient preference information about bleeding, but it seems like the section from page 53-71 does not differential well between side effects of treatment which did not alter course, and minor versus serious side effects or unintended outcomes, which are truly harms of the decision to treat.	Side effects are signs or symptoms that the patient/participant/care provider can detect (and report) which they associate with the medication, and which are undesirable. Harm is a larger umbrella which includes both side effects and negative consequences (both appreciated and unappreciated by the patient/provider). For example, cost to a healthcare system for an ineffective test can be a harm as well as occult valvular heart disease that will not be manifest until time has passed on the drug. It would be desirable to have literature that includes women's perceptions of the relative level of distress over side effects or harms and how/if this modified management. This is why we report the proportion of trial arms that discontinued study drug. We are constrained by the content of the literature and rather than attempting to group as major and minor, have described all the harms associated with the interventions as reported in: 1) The included RCTS 2) Surveillance literature 3) Package inserts for the specific drugs 4) Systematic reviews of the intervention In this way women and care providers can use their individual judgment about the degree to which the potential harms are concerning to them.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Clarity and Usability	Finally, the specific questions that made it to the research needed section do not seem to reflect some of the biggest evidence gaps. Some are very specific. For example, "exploiting large payer data sets" is mentioned as the sole question for Tranexamic Acid, and no cost or use focus using these kind of data are proposed for other therapies. A more systematic approach to patient centers comparative effectiveness priorities should be used in this section of the report.	Excellent point. We have added the suggested areas for research and noted the importance of patient-centered outcomes. We have already noted the importance of an "overall shift towards effectiveness from efficacy, moving beyond the level of proof of concept that is required for drug and device approval to a deeper level that can better inform care, cost considerations, and policy." Specific study concepts like that for TXA are offered as examples and this is noted: "While the number of informative studies that could be designed is likely limitless, we list examples, grouped by indication and intervention, of types of studies that could resolve current and pressing gaps in knowledge." A number of other specific agents are used as examples for other types of studies. The list, as noted, is illustrative and not exhaustive.
Peer Reviewer #4	Clarity and Usability	In my view the report is very well structured and organized, with key findings followed by considerable detail. It will be very important for providing clinicians in making treatment choices for their patients.	Thank you, we hope it will be useful.
Peer Reviewer #6	Clarity and Usability	The Abstract and Executive Summary highlight the review's most important findings. Readers desiring the next level of detail can read the Key Points sections of Results and the Discussion. Those desiring even more detail can read the full report.	Glad we have achieved the desired level of nesting of detail. Thanks for your review.