Evidence-based Practice Center (EPC) Systematic Review Protocol

Project Title: Primary Care Management of Abnormal Uterine Bleeding (AUB)

I. Background and Objectives for the Systematic Review

Problem bleeding is among the most common gynecologic complaints of reproductive age women in ambulatory care settings—of similar frequency to the number seeking care for urinary tract infections and vaginitis. In the general population, abnormal uterine bleeding is estimated to affect 11 to13 percent of reproductive age women at any given time; this prevalence increases with age, reaching 24 percent in those ages 36 to 40 years.[1, 2] In addition to gynecologists, all primary care practitioners including pediatricians, family physicians, advanced practice nurses, and internists, will encounter the need to evaluate, treat, or refer women with bleeding-related symptoms.[3] Women generally present because the amount, timing, or other characteristics of the bleeding have changed from their individual norm.

Population norms for menstrual bleeding, as established by 5th and 95th percentiles, are[4-7]:

- Frequency of menses within a 24 to 38 day window
- Regularity (cycle-to-cycle variation) within ± 2 to 20 days
- Duration of flow from 4 to 8 days
- Volume of blood loss from 5 to 80 ml

Symptoms outside this normal range, or different from normal for the individual, can become problematic and deserve evaluation whether or not they cause difficulties. Common problems include worry about the cause, embarrassment if the bleeding includes flooding type bleeding with saturation of clothing, missed work and responsibilities, limitations of social activities and exercise, decreases in sexual activity, and frustration with costs of sanitary protection.[1, 8] Collectively, the effects of troublesome bleeding reduce quality of life and drive desire for information about causes and treatment options.[1, 8]

There is not a clear consensus on the clinical evaluation of a patient presenting with abnormal bleeding. Recommendations suggest that initial evaluation confirm the source and timing of bleeding, and exclude certain architectural etiologies, cancer, and systemic disease. The International Federation of Gynecology and Obstetrics (FIGO) classification recommends a structured history followed by uterine evaluation.[9] Diagnostic approaches are not within the scope of this review[10, 11]; however, the review will capture the operational definitions and address applicability in the analysis of the relevant literature.

Abnormal uterine bleeding is a diagnosis of exclusion in which there is abnormal bleeding (i.e., quantity, frequency, duration, or regularity) from the uterus not caused by pelvic disease, uterine fibroids, ovarian cysts, endometrial polyps, coagulation disorders, malignancy, inflammation, medical illness, or pregnancy.

The proposed review will hone in on the evidence available to inform selection of nonsurgical options to treat abnormal uterine bleeding 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. We aim to address abnormal bleeding that is chronic in nature, meaning the symptom has persisted for the majority of the prior three months, and is of two primary and common types: (1) irregular in timing (i.e., acyclic); and (2) abnormal though cyclic. Before covering more details about rationale and proposed methods, it is important to establish a common vocabulary that reflects current standards in the related clinical and research areas.

Nomenclature to classify symptomatic problem bleeding has evolved steadily over the past several decades.[12] Early classifications primarily used characteristics of the bleeding to group women. Terms like menorrhagia (abnormally long or heavy menses) and metrorrhagia (bleeding at irregular intervals), were often linked with timing (short or long intervals) and amount (heavy or light) to infer whether or not regular and predictable ovulation was occurring and further assign likely ovulatory or anovulatory status. These terms are generally applied without formal documentation of ovulatory status. Furthermore, previously applied terms like dysfunctional uterine bleeding also carried a variable element of recognition that the label was a diagnosis of exclusion.[12] The resulting challenge was that practitioners and researchers applied different exclusions before selecting interventions or enrolling patients. Over time, differences in terminology choice and in operational definitions resulted in wide inconsistencies in application of diagnostic terms.[4, 12-14]

Recent international consensus recommendations more consistently align terminology by creating two major groupings (i.e., discrete structural vs. nonstructural) for causes of bleeding. The FIGO classification includes nine categories of abnormal bleeding arranged according to the acronym PALM-COEIN[9, 15]: four have objective visual criteria detected by imaging, biopsy, or pathology (i.e., PALM: **p**olyps; **a**denomyosis; **l**eiomyomata; and **m**alignancy and hyperplasia) while another five are not directly related to structural abnormalities (i.e., COEIN: **c**oagulopathy; **o**vulatory dysfunction; **e**ndometrial; **i**atrogenic; and **n**ot yet classified).

The proposed comparative effectiveness review will address the groups characterized by this recently adopted nomenclature as ovulatory dysfunction and endometrial. The relevant population includes nonpregnant women from menarche to menopause who have had abnormal bleeding for three months or longer and have undergone evaluation to rule out structural abnormalities, systemic illnesses and medications as potential causes.

While some reviews further subdivide women experiencing abnormal uterine bleeding into age groups,[16] such as those near menarche and in the perimenopausal timeframe, we plan to retain an emphasis on categorization. Women across the reproductive lifespan can have abnormal bleeding that arises from ovulatory dysfunction or endometrial processes.[17] While the underlying causes may vary, for instance from lack of consistent regulation of the hypothalamic-pituitary-ovarian axis in teens near the onset of menses, and from lack of ovarian reserve in perimenopausal women, the treatment options overlap.[3] We will report when research was done with an age restricted population but will otherwise cover all the relevant literature regardless of reproductive age or reproductive history of participants.

Current practice patterns–In a recently published research article, Matteson and colleagues[18] examined the practice patterns and attitudes from a United States sample of obstetricians and gynecologists regarding the medical treatment of women with AUB. The authors reported that practicing obstetrician-gynecologists most frequently selected combined oral contraceptives for the treatment of both ovulatory and anovulatory heavy menstrual bleeding

and that participants lacked an overall awareness of current evidence on effectiveness of common treatment options for AUB.[18]

Nonsurgical treatment options–Pharmacologic therapies used for treatment of AUB in the ambulatory setting include estrogens, progestogens, combination (estrogen and progestogen) hormonal formulations, nonsteroidal anti-inflammatory drugs, antifibrinolytics, and gonadotropin releasing hormones. Medical interventions are generally considered first line treatment.[19, 20] Surgical intervention is usually reserved for women with persistent bleeding that does not respond to medical therapy or for women who have finished childbearing and do not wish to indefinitely continue medical therapy.[2, 21]

Current recommendations from professional societies including the American College of Obstetricians and Gynecologists (ACOG),[22-25] the American Academy of Family Physicians (AAFP),[21] and the National Institute for Clinical Excellence (NICE)[26] include oral contraceptives, progestins, NSAIDs, levonorgestrel IUD, and antifibrinolytics for management of irregular bleeding and abnormal cyclic bleeding.

Combined oral contraceptives are commonly used to manage abnormal bleeding associated with ovulation. The American College of Obstetrics and Gynecologists 2010 Practice Bulletin for noncontraceptive uses of hormonal contraceptives recommends combined oral contraceptives as a reasonable choice to regulate and reduce menstrual bleeding, based on good and consistent scientific evidence.[24] However, according to a 2009 Cochrane systematic review,[27] there is insufficient evidence to establish the effectiveness of the oral contraceptive pill compared with other medical therapies, placebo, or no therapy for the treatment of heavy menstrual bleeding.[27] In a clinical review for diagnosis and management of abnormal uterine bleeding,[20] authors assert that combined oral contraceptives are likely beneficial for treatment of anovulatory (i.e., acyclic) abnormal uterine bleeding but there is lack of good quality data to support their use in cyclic abnormal bleeding.[20] The combined oral contraceptive is also known to cause abnormal bleeding patterns. Information is needed about the number needed to treat (NNT) for women with AUB and the number need harm (NNH) for adverse effects.

Tranexamic acid therapy–Tranexamic acid, a competitive inhibitor of plasminogen activation, may be useful in women who either desire immediate pregnancy or for whom hormonal treatment is inappropriate. Tranexamic acid appears to be well-tolerated and cost-effective, reducing blood loss considerably and improving health related quality of life for women with menorrhagia.[28]

Levonorgestrel intrauterine system (LNG IUS)–A systematic review of the LNG IUS that pooled data from five prospective RCTs reported that the LNG IUS provided clinically and statistically significant sustained reductions in menstrual blood loss.[25, 29-31]

Complementary and alternative medicine (CAM)–Initial literature scans suggest that there is an extremely limited body of literature on trials of complementary and alternative medicine for AUB. Complementary and alternative medicine based therapies are included as interventions of interest due to their increasing popularity among patients and growing interest to clinicians.[32] A systematic review published in 2009,[33] sought trials of Chinese herbal medicines for the treatment of dysfunctional uterine bleeding. Authors noted that three of the four qualifying studies were assessed to be of poor methodological quality.[33]

Summary– The literature reflects various management options for women with abnormal uterine bleeding (AUB) with conflicting recommendations/summaries. Interventions of interest for this review include medical, complementary and alternative medicine (CAM), and

behavioral/lifestyle interventions. The proposed review will not consider surgical interventions for abnormal uterine bleeding, as surgical management is adequately covered by other groups conducting systematic reviews.

A high quality systematic review that evaluates both irregular and cyclic abnormal uterine bleeding is needed. A review could be used as a foundation for guideline development and to address gaps in the literature.

The proposed report will focus on interventions, especially direct comparisons among treatments that are often used and promoted as first-line choices, with the goal of clearly establishing their effectiveness and potential harms. Interventions that are largely reserved for use in the context of specialized referrals or following the failure of multiple prior interventions will not be included. The proposed report will not evaluate evidence for older compounds that are no longer commonly prescribed for related indications (e.g., the synthetic androgen–Danazol) nor for drugs that modify sex steroid production/signaling (e.g., gonadotropin releasing hormone agonists, selective hormone receptor modulators).

II. The Key Questions

The Key Questions evolved from the EPC team discussions, expert input, and reviewer comments during the topic refinement period and reflect the unmet need for a relevant synthesis of evidence on nonsurgical interventions for abnormal uterine bleeding. We received no comments regarding the Key Questions during posting for public comment. The Key Questions address nonsurgical therapeutic approaches (i.e., medical management, behavioral changes, complementary and alternative medicine) that may be valuable to the provider seeking a first-line approach that minimizes harms. Key question one is subdivided in order to address two types of abnormal uterine bleeding: a) irregular (i.e., noncyclic uterine bleeding); and b) abnormal cyclic uterine bleeding.

Key Question 1A: What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine (CAM) interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular uterine bleeding?

Key Question 1B: What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine (CAM) interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic uterine bleeding?

Key Question 2: What are the harms, including adverse events, associated with medical, behavioral, and complementary and alternative medicine (CAM) interventions (e.g., hormonal treatment, weight loss, or acupuncture) in women with irregular uterine bleeding or abnormal cyclic uterine bleeding?

III. PICOTS Criteria

The populations, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest for the proposed comparative effectiveness review are described in Table 1. The table

includes broad categories of nonsurgical interventions likely to be of interest to women with AUB and to clinicians who evaluate and treat AUB.

Table 1. PICOTS Criteria

PICOTS Element	Description
Population:	Nonpregnant women from menarche to menopause who have had abnormal bleeding for three months or longer whose bleeding is not caused by structural abnormalities, systemic disease, cancer, or medication. Two specific subtypes of abnormal bleeding will be the focus: • *Irregular uterine bleeding:* problem bleeding of three months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease. • *Abnormal cyclic uterine bleeding*: problem bleeding of three months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease.

Interventions[1]:	• Medical therapies
	  ○ Nonsteroidal anti-inflammatory drugs
	  ○ Antifibrinolytics
	  ○ Oral hormone treatments (e.g., oral contraceptives, progestins)
	  ○ Levonorgestrel intrauterine system
	  ○ Vaginal ring contraceptive device
	• Behavioral strategies (e.g., stress reduction, weight reduction, exercise)
	• Complementary and alternative medicine (CAM) therapies (e.g., acupuncture, herbal medicine)

Comparator:	Direct comparison among interventions listed above or comparison to placebo.
Outcomes:	• Bleeding profile (e.g., amount, frequency, duration, pattern, symptom bother, hematocrit) • Quality of life including both bleeding specific and general quality of life measures • Pain related to bleeding • Sexual function as reported by sexual function measures, general measures of sexual activity, frequency and satisfaction • Patient satisfaction with outcomes and acceptability of treatment • Fertility • Time to conception • Additional interventions including concurrent and consecutive surgical and nonsurgical treatments • Harms[2] (e.g., thromboembolic events, emotional side effects, weight gain, short- and long-term harms)
Timing:	Interventions initiated after symptoms have been present most months for three months or longer.
Setting:	Research populations that are applicable to care of women receiving evaluation and treatment in primary care settings including general gynecology.

[1] Surgical interventions and procedures such as endometrial ablation are excluded.
[2] Includes treatment-related adverse events (e.g., drug side effects); does not include consequences related to the failure to adequately treat the symptom.
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The review will focus on interventions, especially direct comparisons among treatments that are often used and promoted as first-line choices, with the goal of clearly establishing their effectiveness and potential harms. An expanded list of interventions identified from the literature is outlined in Table 2.

Treatments with older compounds that are no longer commonly prescribed, such as the synthetic androgen Danazol, as well as drugs that modify sex steroid production or signaling, such as gonadotropin-releasing hormone agonists and selective hormone receptor modulators, are excluded as they are likely to be considered in the context of specialized referrals or when multiple previous interventions have failed.

Table 2 lists specific interventions that were identified in preliminary literature searches and interventions likely to be of interest to clinicians. The list is not exclusive. We will address and include, as appropriate, nonsurgical interventions identified from systematic literature searches (see Appendix A) of medical, lifestyle/behavioral, and CAM therapies for abnormal uterine bleeding. Specific interventions not named in Table 2 that may be located in a literature search will most likely be a CAM strategy/agent or a hormonal agent.

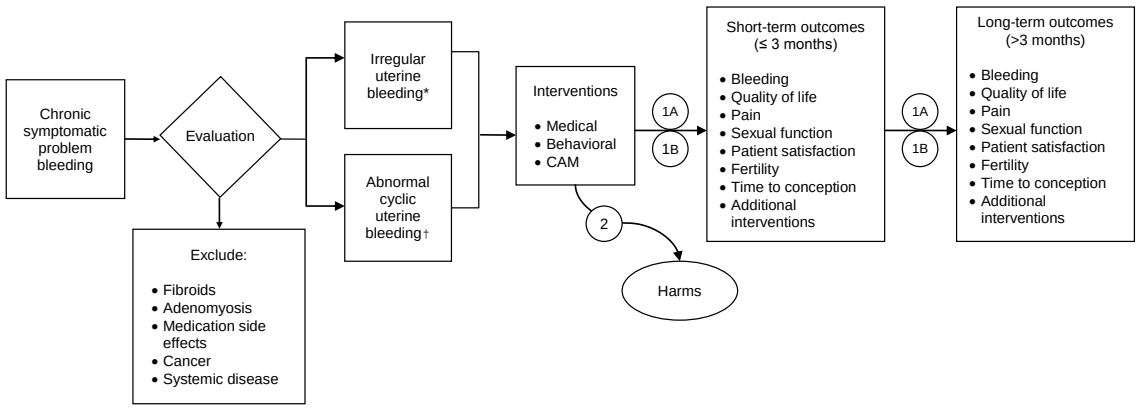
Table 2. Interventions for Abnormal Uterine Bleeding

Nonsteroidal anti-inflammatory drugs (NSAIDs)
• Ibuprofen (e.g., Advil®, Motrin®) • Flurbiprofen (Ansaid®) • Meclofenamate sodium (Meclomen®) • Mefenamic acid (Ponstel®) • Naproxen sodium (e.g., Aleve®, Anaprox®, Naprosyn®)
Antifibrinolytics
• Aminocaproic acid (EACA, Amicar®) • Tranexamic acid (AMCA, Lysteda®, Cyklokapron®)
Hormonal
Progestogens • Medroxyprogesterone (Provera®, Depo-Provera®) • Micronized progesterone (Prometrium®) • Etonogestrel (Implanon®) • Norethindrone acetate (Aygestin®) • Norethindrone (Camila®, Errin®, Jolivette®, Nor-QD®, Nora-BE®, Ortho Micronor®) *Devices* • Levonorgestrel intrauterine device (Mirena®) • Etonogestrel/ethinyl estradiol vaginal ring (NuvaRing®) • Norelgestromin/Ethinyl estradiol transdermal patch (Ortho Evra®) *Combined Estrogen–Progestin Contraceptives* • Ethinyl estradiol/Norethindrone (e.g., Aranelle®, Estrostep®, Junel®, Loestrin®, Microgestin®, Ortho-Novum®, Ovcon®, Tri-Norinyl®) • Ethinyl estradiol/Desogestrel (Desogen®, Ortho-Cept®) • Ethinyl estradiol/Norgestimate (MonoNessa®, Ortho Tri-Cyclen®, Ortho Tri-Cyclen® Lo, Ortho-Cyclen®, Sprintec®, Tri-Sprintec®, TriNessa®) • Ethinyl estradiol/Ethynodiol diacetate (Demulen®, Zovia®, Kelnor®)
Lifestyle/Behavioral
• Stress reduction • Weight loss • Diet/nutrition
Complementary and Alternative Medicine (CAM)
• Acupuncture • Chinese herbal medicine • Phytotherapy

IV. Analytic Framework

The analytic framework illustrates the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis. Input from the key informants was crucial in shaping the analytic framework. No comments related to the framework were received during the public posting phase. (See Appendix B for the alternate text description.)

Figure 1. Primary care management of abnormal uterine bleeding



**Problem bleeding for 3 months or longer, excluding regular cyclic/menstrual patterns of bleeding and bleeding associated with fibroids, polyps, adenomyosis, cancer, medication side effects, and related systemic disease.*

†Problem bleeding for 3 months or longer, excluding irregular and unpredictable patterns of bleeding and bleeding associated with fibroids, polyps, adenomyosis, cancer, medication side effects, and related systemic disease.

Abbreviations: CAM = complementary and alternative medicine

V. Methods

The methodological approaches that will be used for the review are described below.

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

To be considered for inclusion, studies must explicitly define and describe the study population, the interventions, and outcomes. For the proposed comparative effectiveness review, the population of interest includes women with symptomatic cyclic or irregular problem bleeding of three months or longer duration. The population of interest excludes individuals with abnormal uterine bleeding that is caused by systemic disease (e.g., thyroid disease, coagulopathy), structural abnormalities (e.g., fibroids, adenomyosis), cancer, or medication side effects. We will, however, include studies of populations of patients with abnormal uterine bleeding of mixed or ill-defined etiologies. We will review these studies for evaluable data from patients meeting the description of the population of interest (see Table 1). To be considered for inclusion, clinical research studies must evaluate a nonsurgical intervention, (Table 2 above). For all Key Questions, we will include data from controlled clinical trials (e.g., randomized controlled trials) designed to evaluate an

intervention or treatment strategy for individuals from the population of interest. For Key Question 2, we will also include data from uncontrolled observational studies, namely high-quality, large cohort studies, post-marketing surveillance studies, and registries/databases, to capture information on adverse events or other harms.[34] To balance resources and focus on literature of most immediate relevance to primary care practice in the United State, we will exclude papers that are not published in English.[35] Exploratory literature searches using the search terms in this protocol reveal this approach excludes very few if any RCTs that would otherwise have been eligible. We will not stipulate a minimum study sample size for included clinical research studies. Several factors, including varying prevalence of cyclic and irregular patterns of abnormal uterine bleeding, the large number of interventions under consideration for this review, make it difficult to reliably establish a minimum sample size for evaluating treatment effectiveness. Eligible studies must, however, establish and include a sufficient number of study participants to appropriately detect a clinically important difference (i.e., effect size) if such a difference exists for the primary outcome. Ideally, studies will include an explanation of the sample size analysis (e.g., power calculation), identify the primary outcome, and explicitly state the number of participants enrolled in the study. Assessments of individual study eligibility based upon sample size will be conducted and fully described in the methods section of the evidence report. Additional specific criteria for inclusion are noted in Table 3.

Table 3. Inclusion criteria

Category	Criteria
Study population	Nonpregnant women from menarche to menopause experiencing abnormal bleeding for three months or longer and meeting other population criteria from the PICOTS table above.
Time period	Studies published in or after 1980
Admissible designs	• For Key Question 1A and Key Question 1B, eligible study designs must include a relevant comparison group (i.e., comparison of different treatments, treatment vs. no treatment). The following designs will be considered for inclusion: randomized controlled trials • For Key Question 2, eligible study designs will include those noted for Key Question 1A and Key Question 1B and uncontrolled observational studies (e.g., large cohort studies, post-surveillance data studies, and registries/databases of sufficient size to detect harms occurring in one percent of more of individuals exposed)
Other criteria	• Published in English • Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results • For Key Question 1A and 1B, studies must evaluate an intervention (i.e., studies on prevalence, etiology, diagnosis will be excluded) • Studies that evaluate surgical (e.g., hysterectomy) or invasive (e.g., ablation) interventions will be excluded

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- Studies must include at least one outcome measure for an outcome listed in the PICOTS
- Relevant outcomes must be extractable from data presented in the paper
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B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions –

Sources: To ensure comprehensive retrieval of relevant research we will search the following key databases: PubMed, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and EMBASE. We will employ additional searches of the reference lists of related systematic reviews and meta-analyses. We will review the reference lists and methodology, and incorporate into the report discussion as appropriate. The investigative team will also scan the reference lists of articles undergoing full-text review for citations potentially meeting inclusion criteria and screen references suggested by experts, peer reviewers, and the public for potential inclusion or background.

Gray literature: The *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[36, 37] recommends assessment and inclusion of gray literature to minimize bias resulting from selective outcome reporting and publication bias. In addition to searching for published literature, we will conduct a broad search of the gray literature including meeting abstracts, regulatory information, and reports, with a specific focus on with respect to data on harms.[36] We will also seek suggestions from the Technical Expert Panel (TEP) with regard to additional potential sources of gray literature. We will incorporate relevant information from gray literature searches into the review as appropriate (i.e., for assessing publication bias or selective outcomes reporting).

Search strategies: Search strategies will include a combination of terms and keywords related to abnormal uterine bleeding and treatment strategies (Appendix A). A critical component of the search strategy is identification of an exhaustive list of terms used to describe AUB and a more detailed set of descriptors representing the specific subtypes (i.e., abnormal cyclic uterine bleeding and irregular uterine bleeding). We will update search results quarterly during the screening process and conduct a search update upon submission of the draft report.

Limits: We will restrict the search to studies from 1980 forward in order to ensure literature is relevant to current secular trends in practice as well as available treatment strategies. Search strategies will also employ limits to

exclude non-English materials, animal studies, and non-research publication types (e.g., reviews, letters, commentaries, editorials, etc.).

C. Data Abstraction and Data Management –

We will develop screening forms for the literature abstract and full-text review, and data collection forms for data extraction. The team will test the screening and abstraction forms on multiple articles before beginning the abstraction and review process. Screening and data collection forms may undergo revisions following input from the technical expert panel and testing by the team. These forms will be adapted for use in the web-based systematic review product, DistillerSR (Evidence Partners, Ottawa, Canada).

The abstract review form will contain questions about the primary inclusion and exclusion criteria. The full-text review form will include more detailed criteria in order to verify qualifying studies and sort studies according to key question, intervention, and outcomes. We will develop data extraction forms to facilitate data synthesis and create uniform evidence tables. Data extraction forms will collect those data related to population characteristics, type of abnormal bleeding, intervention characteristics, and outcomes including harms. We will evaluate ability to capture data across publications about candidate effect modifiers and confounders of treatment response and uniformly extract those which can be identified in at least 10 percent of publications. Candidate effect modifiers and confounders will include age, body mass index, current and prior contraception, perimenopausal status, fibroid status and comorbidities including diabetes and polycystic ovarian syndrome.

D. Data Synthesis –

Evidence tables: We will enter data into evidence tables by using predetermined abbreviations and acronyms consistently across all entries. The evidence tables will contain common elements such as author, year of publication, study location (e.g., city, state), enrollment period, population description, sample size, and study type (e.g., RCT, prospective observational study). The evidence table dimensions (i.e., the columns) may vary by Key Question as appropriate.

Synthesis: We do not plan to conduct quantitative syntheses (i.e., meta-analyses). Four factors inform this decision: 1) wide differences in how the condition being treated is operationally defined across studies; 2) breadth and specificity of study populations ranging from teens to perimenopausal status; 3) large variety of interventions with rare replication of trials using the same or similar interventions; and 4) disparate primary and secondary outcomes measures. However, if there are multiple RCTs of similar interventions in

similar populations with outcomes that can be aligned, we will reconsider the utility of a meta-analysis.[38]

E. Assessment of Methodological Quality of Individual Studies –

Assessing study quality: Two senior staff will independently perform quality assessment of the included studies; disagreements will be resolved through discussion or third party adjudication as needed. The quality of individual studies will be assessed using specific assessment tools for each type of study. We will record quality assessments in tables, summarizing each study. Studies will be given a quality grade of good, fair, or poor per the established criteria for the assessment tools and the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[37] Data from studies that are considered to be fair or good quality will be included in the analysis. Poor studies will be identified but not included in the main synthesis.

Assessment tools: We will use existing tools with established validity and reliability to assess methodological quality of randomized controlled trials and observational studies. Randomized controlled trials will be assessed using the Cochrane Risk of Bias Tool.[39] This tool includes criteria for judging risk of bias for specific elements from five fundamental domains: sequence generation, allocation concealment, blinding, outcome data, and selective reporting.

For observational studies, we will use the Newcastle Ottawa Scale[40] to assess quality from three broad study characteristics: (1) group selection; (2) study group comparability; and (3) the outcome of interest. More specifically, the fundamental criteria for quality assessment of cohort studies will include: representativeness of the cohort, selection of a nonexposed cohort, ascertainment of treatment exposure, outcome of interest, comparability of cohorts, assessment of outcome, adequate duration of followup, and adequate followup of the cohort (i.e., reporting of loss to followup). In conjunction with this standardized quality assessment tool, we will apply quality criteria specific to 'harms' as described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[34, 37]

F. Grading the Evidence for Each Key Question –

Strength of evidence: We will use explicit criteria for rating the overall strength of the evidence on each intervention into qualitative categories (e.g., low, moderate, high, and insufficient). We will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (i.e., from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of

clinical or behavioral knowledge. We will make these judgments for each of the main Key Questions related to specific outcomes as appropriate.

The strength of evidence evaluation will be that stipulated in *the Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[37, 41] which emphasizes the following four major domains: risk of bias (low, medium, high); consistency (inconsistency not present, inconsistency present, unknown or not applicable); directness (direct, indirect); and precision (precise, imprecise) of the evidence. Risk of bias is derived from the quality assessment of the individual studies that addressed the Key Question and specific outcome under consideration. Each key outcome on each comparison of interest will be given an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence will be graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect).[41] When no studies are available for an outcome or comparison of interest, the evidence will be graded as insufficient.

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

G. Assessing Applicability –

We will assess applicability of the results gathered from the literature to the population of women with abnormal cyclic and irregular uterine bleeding according to EPC methods guidance.[42] Assessment of applicability will be done to account for any factors limiting the ability to apply interventions to other populations or other settings, such as inadequate description of the intervention or failure to report followup data. Using the PICOTS framework, we will identify factors that may limit the applicability of individual research studies. Relevant information will be systematically abstracted and we will report judgments about major limitations to the applicability of individual studies. Finally, we will summarize the applicability of the body of evidence and describe key elements from the PICOTS framework that characterize the applicability of a body of studies.

H. Methodological Challenges

Although guidance for international consensus and consistent use of terms and definitions for symptoms, signs, and causes of abnormal uterine bleeding are now available, these recommendations emerged relatively recently. The available literature on abnormal uterine bleeding remains difficult to navigate due to wide variation in the definitions and synonyms historically used to describe the complaint. There is a minimal amount of literature dedicated to the irregular, unpredictable bleeding associated with anovulation. Heavy menstrual bleeding is more prominent within the literature. We anticipate some challenges to the retrieval of a manageable set of citations with clearly defined study populations and uniformly described study groups. Based on a preliminary review of the literature and input from experts during the topic refinement process, studies may lack explicit definitions to describe the study population. Studies may also include mixed populations and/or poorly defined inclusion/exclusion criteria. In preliminary literature searches, only a handful of studies addressed complementary and alternative medicine interventions for abnormal uterine bleeding. We suspect that the total body of literature on complementary and alternative medicine, and lifestyle/behavioral management is limited. Finding, quality rating, and synthesizing harms data are cited as potential challenges to investigators conducting a systematic review of harms data.[43] As a meta-analysis is not likely to be feasible for this review, we will provide narrative non-quantitative synthesis of the available data from original research studies of acceptable quality for nonsurgical treatment of abnormal uterine bleeding.[38] We will group findings and summary tables by population, intervention and outcomes.

VI. References

1. Liu Z, Doan QV, Blumenthal P, et al. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. Value Health. 2007 May-Jun;10(3):183-94. PMID 17532811

2. Marret H, Fauconnier A, Chabbert-Buffet N, et al. Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause. Eur J Obstet Gynecol Reprod Bio. 2010 Oct;152(2):133-7. PMID 20688424

3. Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. Am Fam Physician. 2004 Apr 15;69(8):1915-26. PMID 15117012

4. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.

5. Hallberg L, Hogdahl AM, Nilsson L, et al. Menstrual blood loss--a population study. Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand. 1966;45(3):320-51. PMID 5922481

6. Treloar AE, Boynton RE, Behn BG, et al. Variation of the human menstrual cycle through reproductive life. Int J Fertil. 1967 Jan-Mar;12(1 Pt 2):77-126. PMID 5419031

7. Belsey EM, Pinol AP. Menstrual bleeding patterns in untreated women. Task Force on Long-Acting Systemic Agents for Fertility Regulation. Contraception. 1997 Feb;55(2):57-65. PMID 9071513

8. Matteson KA, Clark MA. Questioning our questions: do frequently asked questions adequately cover the aspects of women's lives most affected by abnormal uterine bleeding? Opinions of women with abnormal uterine bleeding participating in focus group discussions. Women Health. 2010 Mar;50(2):195-211. PMID 20437305

9. Munro MG, Critchley HO, Broder MS, et al.; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011 Apr;113(1):3-13. PMID 21345435

10. Bradley LD. Diagnosis of abnormal uterine bleeding with biopsy or hysteroscopy. Menopause. 2011 Apr;18(4):425-33. PMID 21701428

11. Doubilet PM. Diagnosis of abnormal uterine bleeding with imaging. Menopause. 2011 Apr;18(4):421-4. PMID 21701427

12. Woolcock JG, Critchley HO, Munro MG, et al. Review of the confusion in current and historical terminology and definitions for disturbances of menstrual bleeding. Fertil Steril. 2008;90(6):2269-80. PMID 18258230

13. Rahn DD, Abed H, Sung VW, et al.; Society of Gynecologic Surgeons Systematic Review Group. Systematic review highlights difficulty interpreting diverse clinical outcomes in abnormal uterine bleeding trials. J Clin Epidemiol. 2011 Mar;64(3):293-300. PMID 20705427

14. Fraser IS, Critchley HO, Munro MG, et al. A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. Fertil Steril. 2007 Mar;87(3):466-76. PMID 17362717

15. Munro MG, Critchley HO, Fraser IS; FIGO Working Group on Menstrual Disorders. The FIGO classification of causes of abnormal uterine bleeding. Int J Gynaecol Obstet. 2011 Apr;113(1):1-2. PMID 21316671

16. Hale GE, Zhao X, Hughes CL, et al. Endocrine Features of Menstrual Cycles in Middle and Late Reproductive Age and the Menopausal Transition Classified According to the Staging of Reproductive Aging Workshop (STRAW) Staging System. J Clin Endocrinol Metab. 2007 August 1, 2007;92(8):3060-7. PMID 17550960

17. Heller DS. Pathologic basis for abnormal uterine bleeding with organic uterine pathologies. Menopause. 2011 Apr;18(4):412-5. PMID 21701425

18. Matteson KA, Anderson BL, Pinto SB, et al. Practice patterns and attitudes about treating abnormal uterine bleeding: a national survey of obstetricians and gynecologists. Am J Obstet Gynecol. 2011 May 14 PMID 21737060

19. Samuel NC, Justin Clark T. Future research into abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol. 2007;21(6):1023-40. PMID 17584533

20. Telner DE, Jakubovicz D. Approach to diagnosis and management of abnormal uterine bleeding. Can Fam Physician. 2007 Jan;53(1):58-64. PMID 17872610

21. Ely JW, Kennedy CM, Clark EC, et al. Abnormal uterine bleeding: a management algorithm. J Am Board Fam Med. 2006 Nov-Dec;19(6):590-602. PMID 17090792

22. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin No. 14: management of anovulatory bleeding. Int J Gynaecol Obstet. 2001 Mar;72(3):263-71. PMID 11296797

Source: www.effectivehealthcare.ahrq.gov
Published Online: November 21, 2011

23. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin No. 59: clinical management guidelines for obstetricians-gynecologists: intrauterine device. Obstet Gynecol. 2005 Jan;105(1):223-32. PMID 15625179

24. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. Obstet Gynecol. 2010 Jan;115(1):206-18. PMID 20027071

25. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin No. 121: long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol. 2011 Jul;118(1):184-96. PMID 21691183

26. National Collaborating Centre for Women's and Children's Health. Heavy Menstrual Bleeding. NICE Clinical Guideline CG44. London: Institute for Health and Clinical Excellence; 2007.

27. Farquhar C, Brown J. Oral contraceptive pill for heavy menstrual bleeding. Cochrane Database Syst Rev. 2009(4):CD000154. PMID 19821266

28. Lumsden MA, Wedisinghe L. Tranexamic acid therapy for heavy menstrual bleeding. Expert Opin Pharmacother. 2011 Sep;12(13):2089-95. PMID 21767224

29. Endrikat J, Vilos G, Muysers C, et al. The levonorgestrel-releasing intrauterine system provides a reliable, long-term treatment option for women with idiopathic menorrhagia. Arch Gynecol Obstet. 2011 Apr 8 PMID 21475963

30. Espey E, Ogburn T. Long-acting reversible contraceptives: intrauterine devices and the contraceptive implant. Obstet Gynecol. 2011 Mar;117(3):705-19. PMID 21343774

31. Chattopdhyay B, Nigam A, Goswami S, et al. Clinical outcome of levonorgestrel intra-uterine system in idiopathic menorrhagia. Eur Rev Med Pharmacol Sci. 2011 Jul;15(7):764-8. PMID 21780544

32. Livdans-Forret AB, Harvey PJ, Larkin-Thier SM. Menorrhagia: a synopsis of management focusing on herbal and nutritional supplements, and chiropractic. J Can Chiropr Assoc. 2007 Dec;51(4):235-46. PMID 18060009

33. Tu X, Huang G, Tan S. Chinese Herbal Medicine for Dysfunctional Uterine Bleeding: a Meta-analysis. Evid Based Complement Alternat Med. 2009 Mar;6(1):99-105. PMID 18955223

34. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):502-12. PMID 18823754

35. Avoiding bias in selecting studies. AHRQ Draft Manuscript: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; Published June 23 2011. www.effectivehealthcare.ahrq.gov.

36. Relevo R, Balshem H. Finding evidence for comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1168-77. PMID 21684115

37. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2011. www.effectivehealthcare.ahrq.gov.

38. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1187-97. PMID 21477993

39. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID 22008217

Source: www.effectivehealthcare.ahrq.gov
Published Online: November 21, 2011

40. Newcastle-Ottawa Quality Assessment Scale: Cohort studies. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed on 24 August 2011.

41. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID 19595577

42. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1198-207. PMID 21463926

43. Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. Ann Intern Med. 2005 Jun 21;142(12 Pt 2):1090-9. PMID 15968034

VII. Definition of Terms

- *Irregular uterine bleeding*: problem bleeding of three months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease.
- *Abnormal cyclic uterine bleeding*: problem bleeding of three months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease.

VIII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

IX. Review of Key Questions

The Key Questions were reviewed and refined by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the Key Questions were posted for public comment and finalized by the EPC after review of the comments.

X. Key Informants

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

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

XI. Technical Experts

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

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

XII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

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

XIII. Role of the Funder

This project was funded under Contract No. 290-2007-10065 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the

methodological quality of the report. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

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