Evidence-based Practice Center Systematic Review Protocol

Project Title: Management of Uterine Fibroids

I. Background and Objectives for the Systematic Review

Topic background

Most women will develop one or more uterine fibroids (i.e., leiomyomata), benign smooth muscle tumors of the uterus, during their reproductive lifespan.[1] In the United States, an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.[1-4] More than 15 million of them will experience associated symptoms or health concerns.[5,6] A disproportionate number of black women are among those with symptoms in part due to earlier age at onset of fibroids with larger and more numerous tumors.[1-3,7,8]

The etiology of uterine fibroids is not well understood, and a variety of factors including race/ethnicity, parity, and age at menarche have been examined. Health effects range from profound bleeding and anemia, to pelvic pressure or pain, urinary frequency, abnormal bowel function, and pain with intercourse, as well as concerns about influence on fertility and pregnancy outcomes.[9]

Fibroids are prevalent and symptoms are common among women with fibroids, creating considerable personal and societal costs including diminished quality of life, disruption of usual activities and roles, lost work time associated with symptoms, and substantial healthcare expenditures. Across types of interventions, direct annual healthcare costs in the United States are projected to exceed $9.1 billion. Lost wages, productivity, and short-term disability are estimated to total more than $5 billion, perhaps as much as $17 billion, with roughly $4,624 in costs per women in the first year of diagnosis.[10,11]

Current management

Discussion of options for management of symptomatic fibroids is among the most frequent conversations in gynecology and primary care and is the most common cause for consideration of gynecologic surgical intervention.[12,13] The nature of those discussions is also fundamentally shaped by future reproductive goals and desire to retain fertility.[14,15]

Though hysterectomy and myomectomy by a variety of routes are frequently used, perhaps with insufficient consideration of alternative treatment prior to surgery,[16] the range of fibroid-specific treatments including interventions like extended medical management with ulipristal acetate, magnetic resonance image-guided focused ultrasound (MRgFUS), uterine artery embolization, radiofrequency volumetric thermal ablation, and techniques for myolysis are increasingly generating comparative effectiveness data[7,9] as is the clinical trials literature about improving bleeding symptoms.[17] Furthermore, as the literature evolves, including larger studies of stronger design with longer followup, a clearer picture of anticipated outcomes is likely to emerge.

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No medications have been specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of fibroid symptoms, though several medications are used off-label (see Table A-1 in Appendix). The FDA has approved a number of devices to treat uterine fibroids including MRgFUS systems and power morcellators (see Table A-2 in Appendix), though it has issued safety communication for laparoscopic uterine power morcellation.[18]

Across treatment modes attention should be paid to the influence of the characteristics of individual women and their fibroids in predicting outcomes and judging whether differing interventions are differentially influenced by such factors as fibroid size, location, and the patient's contraceptive choices or age. Women desire a broad range of treatment options that suit their life circumstances and future reproductive desires. Therefore, it is crucial for women, their care providers, and those who guide policy decisions to have timely, accurate information about the effectiveness of treatments and the associated risks.

What this review will add to the body of literature

The quantity and quality of research on fibroid management has steadily improved in recent years. It should now be feasible, and most informative to guiding care, to restrict a review to randomized clinical comparisons of effectiveness, including medical management versus surgical, rather than restricting comparisons only to abdominal hysterectomy. Specifically this review will address the recent visibility and uncertainty about the harms of morcellation of fibroids during minimally invasive procedures, as an explicit element of risk of harm.

II. The Key Questions

The Key Questions evolved from the EPC team discussions, expert input, and reviewer comments during the topic refinement period. The Key Questions reflect the unmet need for a relevant synthesis of evidence from prospective randomized controlled trials on the relative benefits and harms of surgical, procedural, and medical interventions to manage uterine fibroids. In addition, the Key Questions address the potential harms associated with morcellation, as well as an exploration of patient and tumor characteristics that may predict success or adverse events in patients considered for morcellation.

Key Question 1. What is the comparative effectiveness (benefits and harms) of treatments for uterine fibroids, including comparisons among and within these interventions?

- Hysterectomy via abdominal, vaginal, laparoscopic, or robotic approach;
- Myomectomy via laparotomy, laparoscopy, hysteroscopy, or robotic approach;
- Uterine artery embolization including ligation and occlusion;
- Ablative procedures (e.g., MRgFUS, cryoablation);
- Progestin-containing intrauterine devices;
- Medications to improve or resolve symptoms or reduce size of fibroids;
- Expectant management or placebo

Key Question 2. Does treatment effectiveness differ by patient or fibroid characteristics (e.g., age, race/ethnicity; symptoms; vascular supply to fibroids; menopausal status; or number, size, type, location, or total volume of fibroids)?

Key Question 3. What is the risk of cancer dissemination from morcellation of uterine fibroids at the time of myomectomy or hysterectomy?

Key Question 4. Does risk of cancer dissemination from morcellation differ by patient or fibroid characteristics (e.g., age; race/ethnicity; symptoms; menopausal status; imaging characteristics; vascular supply to fibroids; or number, size, type, location, or total volume of fibroids)?

Public Comments and Changes to Posted Key Questions

The draft Key Questions were posted for public comments (6/23/15 – 7/13/15). Comments did not necessitate any significant changes to the Key Questions, review scope, or inclusion criteria. Minor changes included the addition of fibroid type and location as a characteristic of interest in Key Question 2 and Key Question 4. Additionally, public comments noted the need to assess effectiveness of morcellation in

addition to harms. This comment did not require changes to the Key Questions as literature addressing Key Question 1 would include benefits of morcellation.

PICOTS for Key Questions

Table 1. PICOTS

PICOTS	Criteria and Key Question(s)
Population	• Women who are being treated for uterine fibroids (KQs 1-4)
Intervention(s)	• Surgical (KQs 1-4) • Procedural (KQs 1, 2) • Medical / Pharmacologic (KQs 1, 2) • Morcellation (KQs 1-4)
Comparator	• Inactive treatment including wait list control, expectant management, or placebo • Active treatment
Outcomes	<u>Intermediate outcomes (KQ 1)</u> • Technical success • Conversion to alternate operative procedure • Estimated blood loss • Wound healing status • Length of stay • Readmission/reoperation • Return to usual activities <u>Final health outcomes (KQ 1)</u> • Symptom status • Desired fertility status • Pregnancy outcomes • Sexual function • Fibroid characteristics • Fibroid recurrence • Subsequent treatment for fibroids • Satisfaction with outcomes <u>Adverse effects / Harms (KQs 1, 3)</u> • Transfusion • Unplanned hysterectomy • Perforation of organs • Cancer dissemination • Misdirected embolization / non-target tissue embolization • Ovarian failure • Other serious adverse events
Timing	Any length of followup (KQs 1-4)
Setting	Clinical setting in countries with health care systems similar to the U.S. (defined as inclusion as a Very High Human Development country on the United Nations Development Programme Human Development Index (KQs1-4) *Countries include: Albania, Algeria, Andorra, Antigua and Barbuda, Argentina, Armenia,*

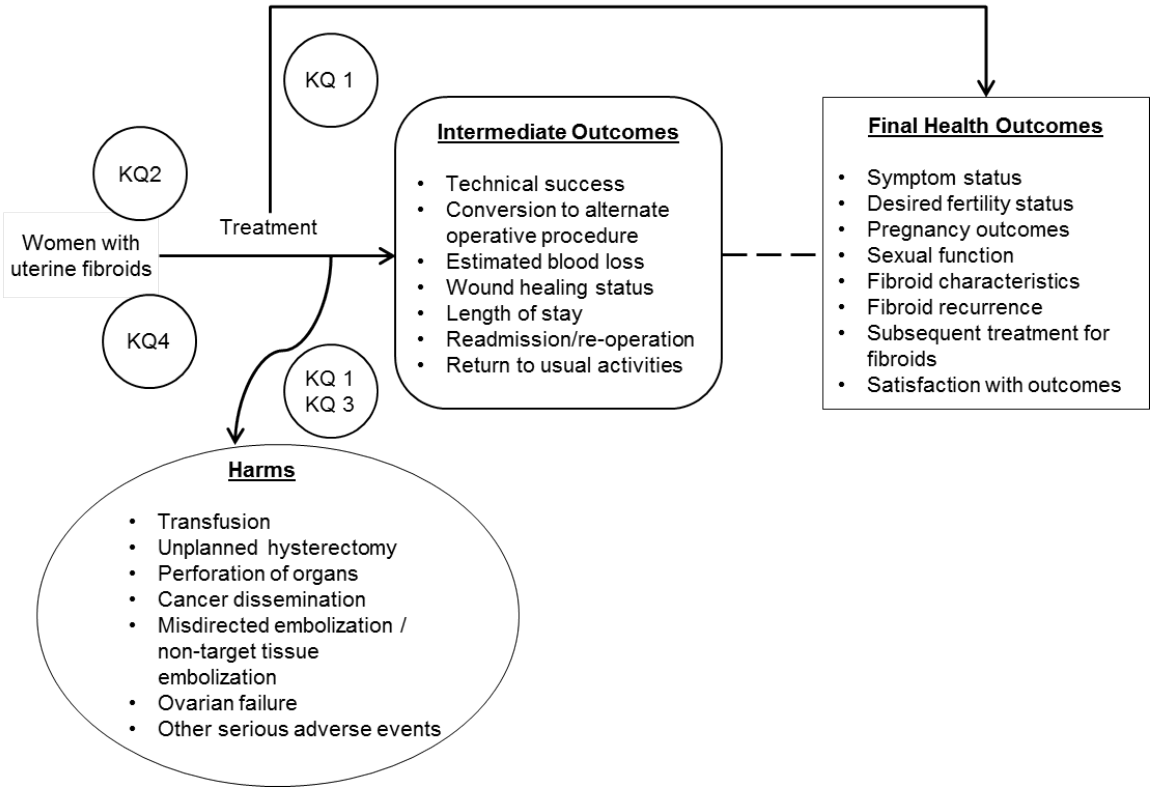
PICOTS	Criteria and Key Question(s)
	Australia, Austria, Azerbaijan, Bahamas, Bahrain, Barbados, Belarus, Belgium, Belize, Bosnia and Herzegovina, Brazil, Brunei Darussalam, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Dominica, Dominican Republic, Ecuador, Estonia, Fiji, Finland, France, Georgia, Germany, Greece, Grenada, Hong Kong, China (SAR), Hungary, Iceland, Iran (Islamic Republic of), Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kazakhstan, Korea (Republic of), Kuwait, Latvia, Lebanon, Libya, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Mexico, Montenegro, Netherlands, New Zealand, Norway, Oman, Palau, Panama, Peru, Poland, Portugal, Qatar, Romania, Russian Federation, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Saudi Arabia, Serbia, Seychelles, Singapore, Slovakia, Slovenia, Spain, Sri Lanka, Suriname, Sweden, Switzerland, Thailand, The former Yugoslav Republic of Macedonia, Tonga, Trinidad and Tobago, Tunisia, Turkey, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, Venezuela

Abbreviations: KQ=key question;

III. Analytic Framework

The analytic framework illustrates the population, interventions, outcomes, and adverse effects that guide the literature search and synthesis.

Figure 1. Analytic framework for treatment of uterine fibroids



IV. Methods

The methods for this systematic review will follow the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[19] and the PRISMA-P[20] statement checklist. The protocol is registered in Prospero (CRD42015025929).

Inclusion and Exclusion of Studies in the Review

This review will include studies evaluating medical and surgical treatments to treat fibroids (asymptomatic or symptomatic) in women of any age. There is some literature about the relationship of imaging findings and symptom profiles, but the correlation is not tight. Women with large fibroids may experience minimal symptoms while women with small fibroids may have significant symptoms. Diagnostic accuracy and sequencing of care are outside of the scope of this review. Ongoing observational studies such as COMPARE[21] will provide data about sequencing of treatments when completed. We do not anticipate that current studies can offer meaningful data to address a sequencing question.

The review will focus on interventions to treat fibroids directly. Prior reviews have reported on the effectiveness preoperative adjunctive treatments such as gonadotropin-releasing hormone (GnRH) agonists or cell savers. Such approaches are generally well accepted in practice. This review will not include studies that evaluate the effectiveness of preoperative or adjunctive interventions to minimize blood loss or otherwise improve operative outcomes.

Randomized controlled trials are best suited to provide data for comparative effectiveness and there has been substantial growth in the variety and sophistication of trials since the prior review. Therefore, eligible studies for Key Question 1 and Key Question 2 must be randomized trials evaluating the benefits or harms of a medical, procedural, or surgical intervention compared with an inactive control, including expectant management, or alternate intervention. We will include nonrandomized cohort studies and observational studies to address Key Question 3 or Key Question 4.

Key Question 1 and Key Question 2 focus on comparative effectiveness for final outcomes. Eligible studies must report one or more patient-centered outcome (e.g., symptom improvement, blood loss, pain, quality of life). Studies reporting only outcomes related to healthcare delivery (e.g., costs, access) will not be included. Cost data are linked with operative time and clinician skill sets, which may be affected by a number of factors. Older cost data also have limited utility. Studies reporting only intermediate outcomes will not be included.

A preliminary assessment of the published literature on uterine fibroid treatment suggests that limiting the search to studies published in or after 1985 does not omit critical literature. We summarize the inclusion criteria in Table 2.

Table 2. Inclusion criteria

Category	Criteria
Population	Women with uterine fibroids (KQs 1-4)
Design	• Randomized controlled trial (KQs 1, 2) • Any (KQs 3, 4)

Other	• Original research (KQs 1-4)
	• Publication language: English (KQs 1-4)
	• Publication year: 1985-2015 (KQs 1-4)
	• Reports one or more:
	  ○ Uterine fibroid treatment/intervention outcome (KQs 1, 2)
	  ○ Harm or adverse event from uterine fibroid treatment/intervention (KQs 1-4)
	• Sufficient detail of methods and results to enable data extraction (KQs 1-4)
	• Reports outcome data by target population or intervention (KQs 1-4)

KQ=Key Question

Searching for the Evidence

Published literature

To ensure comprehensive retrieval of relevant studies, we will search MEDLINE via PubMed, the Cumulative Index to Nursing and Allied Health (CINAHL), EMBASE, and the Cochrane Library to identify relevant publications. We will use the search strategies presented in Tables A-3 and A-4 of the Appendix. The search and selection literature sources may be refined following discussions with Technical Experts. The final search strategies will be peer reviewed by an independent information specialist. We will use a date limit of 1985 for the search of indexed literature. We will conduct literature search updates periodically during preparation of the review and will conduct a final literature search update at the time of peer review of the draft report. We will screen and include relevant studies with each update. We will also incorporate relevant, eligible studies identified by peer reviewers or public commenters.

Grey literature

We will search web sites of organizations likely to conduct research, issue guidance, or generate policies relevant to management of uterine fibroids (Table A-5 in the Appendix). We will search government and regulatory agency web sites for information on morcellation. We will search ClinicalTrials.gov for information about relevant ongoing trials and to confirm that we have obtained available publications of results from completed trials.

Hand searching

We will carry out hand searches of the reference lists of recent systematic reviews or meta-analyses of therapies for uterine fibroids. The investigative team will also scan the

reference lists of articles that are included after the full-text review phase for studies that potentially could meet our inclusion criteria.

Scientific Information Packets

The Scientific Resource Center (SRC) will request information from stakeholders, including Scientific Information Packets (SIP) and regulatory information on medications, procedures, and devices used to treat uterine fibroids. We have listed known pharmaceutical companies (Table A-1) and device manufacturers (Table A-2) in Appendix A. We will compare the information in the SIPs with the biomedical literature and grey literature retrieval. We will extract information from the SIPs that is not already captured by published study results or other sources. We will apply the same inclusion and exclusion criteria relevant to Key Questions to studies identified via SIPs.

Selecting Studies

Screening forms

We will develop forms for screening and preliminary data extraction. The form used at the abstract screening level will include basic questions to determine study eligibility based on the exclusion and inclusion criteria. The forms used for the full-text screening level will include additional questions to identify studies that meet all the inclusion criteria. The forms will also include questions to assist in preliminary grouping of the eligible studies by Key Question.

Abstract screening

We will review the titles and abstracts of all publications identified through our searches against our inclusion/exclusion criteria. To be excluded, publication abstracts must be reviewed and excluded independently by two members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion.

Retrieving and reviewing articles

We will retrieve and review all articles that meet our predetermined inclusion criteria from abstract screening or for which we have insufficient information to make a decision about eligibility. Each article will be reviewed for eligibility independently by two members of the investigative team. Differences between the reviewers will be adjudicated by a senior team member or via team discussion. We will use the same screening forms and inclusion/exclusion criteria to assess eligibility of citations recommended by peer and public reviewers and for the literature retrieved by updated literature searches. If we are unable to resolve a discrepancy in the reporting of data from a publication we may contact study authors for additional information or clarification.

Data Management

We will develop a simple categorization scheme for coding the reasons that articles at full review are excluded. We will record exclusion codes in an EndNote® (Thomson Reuters, New York, NY) bibliographic database and will compile a list of excluded papers and

exclusion reasons in the report. We will deposit data used in a meta-analysis into the Systematic Review Data Repository (SRDR).

Data extraction

We will create data extraction forms to collect detailed information on the study characteristics, intervention(s), comparator(s), arm details, reported outcomes and outcome measures, and risk of bias assessment. We will pilot test the data entry forms. We will upload the extracted data to the Systematic Review Data Repository (SRDR).

For studies that meet the eligibility criteria from the full-text review assessment, we will extract study characteristics (e.g., study design, year, setting, funding source, etc.); patient characteristics (e.g., age, race/ethnicity, symptom status, treatment history); operational definition of fibroid; diagnostic modality (e.g., imaging, symptom record); intervention description and characteristics; outcomes of interest reported; operational definition of each outcome; results; and length of followup.

We will extract additional information, when reported, to assess whether the effectiveness of interventions differ by patient or fibroid characteristics. Examples include: baseline characteristics of the patients (e.g., age, menopausal status; symptom status) and fibroid characteristics (e.g., size, volume, location, type, and vascularity).

We will prespecify the harms that we will extract and will use consistent and precise terminology for reporting data on harms to the degree the literature includes operational definitions.[22] We will check sources other than published literature (e.g., FDA, clinical trial data from device manufacturers or pharmaceutical companies via SIPs) for additional information on harms.

Assessment of Methodological Risk of Bias

We will evaluate the methodologic risk of bias of individual studies. We will use the criteria and established tools described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[23] Two senior investigators will assess each included study independently. Disagreements will be resolved through discussion.

We will use prespecified questions[1] from Table 4 in "*Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions*"[23] to assess risk of bias of randomized controlled trials. We will use an adapted version of the McMaster Quality Assessment Scale of Harms tool to assess harms reporting.[23,24] We will enumerate the risk of bias assessments and source of bias for all studies. Depending upon the quantity and size of the sources for the data, we may attempt to establish thresholds to assess overall high, medium or low risk of bias.[25]

We may limit the report of key findings from studies assessed as high risk of bias to summary tables. We may include in the analysis high of risk of bias studies that have a large sample size or that evaluate outcomes not addressed in other studies.

[1] from Table 4 in "Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions".[23]

Synthesizing Results

We will provide a qualitative and quantitative synthesis of studies meeting our review criteria. We will summarize data related to symptom status and prioritize patient-reported measures. We collected a list of outcomes from a prior review of relevant studies and prioritized that list to establish a core minimum set of outcomes for quantitative analyses. We identified patient-centered outcomes including bleeding, pain, other symptom resolution, need for subsequent treatment, and quality of life, as those of greatest priority.

We anticipate performing a meta-analysis to describe the effects of treatment decisions on outcomes including likelihood of maintaining fertility or needing additional treatment, including, ultimately, hysterectomy. The specific meta-analysis or meta-regression will depend on the data available. In particular, we hope to estimate probabilities of an outcome associated with potential trajectories of care for women under differing circumstances (e.g., likelihood of progressing to increasingly invasive options, particularly hysterectomy).

We will refine our analytic approach as we gather more data on the available literature. It is likely that analyses will be combined using a Bayesian hierarchical mixed effects model. Hierarchical random effects allow results from individual studies to be partially pooled, meaning that each study can contribute to inference in the meta-analysis without assuming that the set of studies are identical. These random effects will allow estimates of overall (population) effects as well as an estimate of the variance of the effect across studies, after controlling for available study-level covariates.

Quantifying study-level heterogeneity via random effects is preferable to the use of an arbitrary variance cutoff value or statistical tests for heterogeneity, such as Q statistics or I^2 scores. The decision of whether to partially pool a set of studies using random effects depends not on how heterogeneous their outcomes are, but rather, whether they can be considered exchangeable studies from a population of studies of the same phenomenon. This should be determined based on the design and quality of the studies, independently of the studies' relative effect sizes.

Many fibroid studies have small sample sizes, which limit the ability of a study to overcome differences in baseline characteristics and variability of outcome reporting. Some differences among study populations may be accounted for in the model by adjusting for factors such as age distribution, demographic attributes, and the prevalence of concomitant conditions in the study sample. Newer approaches to random effects meta-analysis, such as latent Dirichlet process and Gaussian process models, allow for robust (e.g., non-parametric) estimates of variation that do not rely on the assumption of normally distributed random effects. This permits us to account for "outlier" studies in the meta-analytic model without either discarding them unnecessarily or allowing them to influence meta-estimates disproportionately.

Analysis of subgroups will be done formally, within a statistical model, or by stratifying results and organizing the report in such a way that end users are provided with overall outcomes data and information specific to subgroups defined by factors such as menopausal status or fibroid size that can be easily identified and stand alone as needed.

Subgroup analysis may be used to evaluate the intervention trajectory in a defined subset of the participants in a trial, or in complementary subsets. Subgroup analysis can be undertaken in a variety of ways, from completely separate models at one extreme, to simply including a subgroup covariate in a single model at the other, with multilevel and random effects models somewhere in the middle. Generally, trial sizes are too small for sub-group analyses within individual studies to have adequate statistical power.

Meta-regression models describe associations between the summary effects and study-level data; that is, it describes only between-study and not between-patient variation. We will use multilevel models, which boost the power of the analysis by sharing strengths across subgroups for variables where it makes sense to do so, or subgroup analysis (with random effects meta-analysis) to explore heterogeneity if there are a sufficient number of studies.

Grading the Strength of Evidence for Major Comparisons and Outcomes

We will use explicit criteria for rating the overall strength of the evidence for intervention-final outcome pairs for which the overall risk of bias is not overwhelmingly high. We will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge.

We will assess strength of evidence as stipulated in the Effective Health Care Program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* updated strength of evidence guide.[25] Current guidance on strength of evidence evaluation emphasizes the following major domains: study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct, indirect), precision (precise, imprecise), and reporting bias (present, undetected). Intervention-outcomes pairs will be given an overall evidence grade based on the ratings for the individual domains.

The assessment of the study limitations domain will be derived from the risk of bias of the individual studies that addressed the Key Question and specific outcome under consideration. The domains of consistency and precision will be assessed based on the direction and variation of the estimates. We will assess reporting bias of randomized controlled trials by examining outcomes of trials as reported in resources such as ClinicalTrials.gov to determine if prespecified outcomes are not reported in the published literature. We assign an overall grade (high, moderate, low or insufficient) for the strength of evidence for each key outcome (Table 4).

Table 4. Strength of evidence grades and definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Two senior staff will independently grade the body of evidence; disagreements will be resolved as needed through discussion or third-party adjudication. We will record strength of evidence assessments in tables, summarizing results for each outcome. When no studies are available for an outcome or comparison of interest, we will grade the evidence as insufficient.

Assessing Applicability

We will assess the applicability of findings reported in the included literature to the general population of women with uterine fibroids by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category.

We anticipate that areas in which applicability will be especially important to describe will include racial/ethnic variability, availability of treatment options, desired fertility status, fibroid characteristics such as size, volume, type, location, and number.

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VI. Definition of Terms

Table 5. Abbreviations and Terms

Acronym	Term
ACOG	American College of Obstetricians and Gynecologists
AF	Analytic Framework
AHRQ	Agency for Healthcare Research and Quality
CAM	Complementary and alternative medicine
CER	Comparative Effectiveness Review
CINAHL	Cumulative Index to Nursing and Allied Health
COMPARE-UF	Comparing Options for Management: Patient-Centered Results for Uterine Fibroids
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
FIGO	International Federation of Gynecologists and Obstetricians
GnRH	Gonadotropin releasing hormone
KI	Key Informant
KQ	Key Question
MRgFUS	Magnetic resonance guided focused ultrasound
NSAID	Non-steroidal anti-inflammatory drug
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, Setting
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomized controlled trial
SERM	Selective estrogen receptor modulator
SPRM	Selective progesterone receptor modulator
SIP	Scientific Information Packet
TEP	Technical Expert Panel
TOO	Task Order Officer
WHO	World Health Organization

VII. Summary of Protocol Amendments

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

VIII. Review of Key Questions

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

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions

for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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

X. Technical Experts

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

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

XI. Peer Reviewers

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

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer

reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

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

XIII. Role of the Funder

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Appendix

Table A-1. Medications for uterine fibroid treatment

Drug Category Drug Name *Brand/Other Names*	Labeled Indications	Company Name Location
GnRH Agonists		
Cetrorelix Acetate *Cetrotide®*	**FDA-labeled indications:** Ovulation induction **Non-FDA labeled indications:** Uterine leiomyoma	**Merck Serono (EMD Serono, Inc.)** **Rockland, MA** **USA**
Goserelin Acetate *Zoladex®*	**FDA-labeled indications:** Breast cancer, For palliation of advanced disease in pre- and peri-menopausal women; Endometriosis; Hypoplasia of endometrium; Prostate cancer, Advanced (palliative treatment) and in combination with flutamide for locally confined stage B2-C disease **Non-FDA labeled indications:** Breast cancer, Adjuvant treatment of hormone receptor-positive, axillary lymph node-positive disease in premenopausal women; Dysfunctional uterine bleeding; In vitro fertilization; Precocious puberty; Prostate cancer	**AstraZeneca Pharmaceuticals** **Wilmington, DE** **USA**
Leuprolide Acetate *Eligard®, Lupron Depot®, Lupron®, Viadur®*	**FDA-labeled indications:** Anemia- uterine leiomyoma (preoperatively with iron); central precocious puberty; endometriosis; advance prostate cancer **Non-FDA labeled indications:** Breast cancer; In vitro fertilization; Ovarian cancer; Premenstrual syndrome; Prostate cancer; Uterine leiomyoma	**AbbVie** **Chicago, IL** **USA**
Triptorelin Pamoate *Trelstar Depot®, Trelstar LA®, Trelstar®*	**FDA-labeled indications:** Prostate cancer, advanced **Non-FDA labeled indications:** Central precocious puberty; Endometrial hyperplasia; Endometriosis; Fibrocystic breast changes; in vitro fertilization; Uterine leiomyoma.	**Actavis** **Parsippany, NJ** **USA** **Watson Pharma** **Morristown, NJ** **USA**
Buserelin *Suprefact®, CinnaFact®, Metrelef®*	*Not available in the US*	**Sanofi-Aventis** **Laval, Quebec** **Canada**
Progesterone Antagonists/Agonists		
Mifepristone *Mifeprex®, RU-486*	**FDA-labeled indications:** hyperglycemia; pregnancy termination **Non-FDA labeled indications:** Dilation of cervical canal; emergency contraception; miscarriage; ovarian cancer	**Danco Laboratories** **New York City** **USA**

Drug Category Drug Name *Brand/Other Names*	Labeled Indications	Company Name Location
Ulipristal Acetate *Ella®*	**FDA-labeled indications:** emergency conception **Non FDA-labeled indications:** Menorrhagia, uterine leiomyoma (preoperative)	**Actavis** **Parsippany, NJ** **USA** **Watson Pharma** **Morristown, NJ** **USA**
Estrogen Receptor Antagonists/ SERM		
Fulvestrant *Faslodex®*	**FDA-labeled indications:** Breast cancer, Invasive, in postmenopausal women; **Non-FDA labeled indications:** first-line therapy in hormone sensitive breast cancer, following disease progression while on an aromatase inhibitor; neoadjuvant therapy in breast cancer in premenopausal women with breast cancer; endometriosis, dysfunctional uterine bleeding; uterine fibroids	**AstraZeneca** **Wilmington, DE** **USA**
Raloxifene Hydrochloride *Evista®*	**FDA-labeled indications:** Breast cancer, Invasive, in postmenopausal women; Postmenopausal osteoporosis **Non-FDA labeled indications:** Disorder of the cardiovascular system	**Eli Lilly and Company** **Indianapolis, IN** **USA**
Other		
Levonorgestrel-releasing intrauterine system *Mirena®, LNG-IUS*	**FDA-labeled indications:** Contraception; emergency contraception; menorrhagia **Non-FDA labeled indications:** Endometrial hyperplasia; Endometriosis; Menopausal symptom	**Bayer Healthcare Pharmaceuticals, Inc** **Whippany, NJ** **USA**
Lynestrenol	*Not approved for use in US*	**NAARI AG** **Switzerland**
Tibolone *Livial*	*Not available in the US*	**Merck Sharp & Dohme Limited** **Hertfordshire** **UK**
Aromatase inhibitors	*Not FDA approved for treatment of uterine leiomyoma*	

Table A-2. Devices for uterine fibroid treatment

Device	Manufacturer
Morcellators	
MORESolution™	BlueEndo
Cook Tissue Morcellator	Cook Urological Inc.
Coring Morcellator	Cook Urological Inc.
Gyncare Morcellex Tissue Morcellator	Ethicon Inc.
Gynecare Laparoscopic Morcellator	Ethicon Inc.
Gynecare Morcellex Tissue Morcellator Models Mx0100 And Mx0100r	Ethicon Inc.
Femrx Morcellator System	Gynecare Innovation Center
Pks Plasma Morcellator Models 962000pk 3620pk	Gyrus Acmi Inc.
Lasersonics Tissue Morcellator Set	Heraeus Surgical Inc.
Ksea Sawahle Electromechanical Morcellator	Karl Storz Endoscopy
Kse Steiner Electromechanic Morcellator	Karl Storz Endoscopy-America Inc.
Ksea Rotocut G1 Electromechanical Morcellator	Karl Storz Endoscopy-America Inc.
Ksea Sawahle Electromechanical Morcellator	Karl Storz Endoscopy-America Inc.
Ksea Steiner Electromechanic Morcellator	Karl Storz Endoscopy-America Inc.
Ksea Steiner Electromechanic Morcellator	Karl Storz Endoscopy-America Inc.
Coherent Tissue Morcellator Kit And Accessories	Lumenis Inc.
Lumenis Versacut Tissue Morcellator System	Lumenis Inc.
Versacut + Tissue Morcellator	Lumenis Ltd.
Morce Power Plus And Variocarve Morcellator	Nouvag Ag
Riwo Cut-Morcellator Existing Of Knife/Cutting Sleeve/Protection Sleeve/Claw Grasping Forceps	Richard Wolf Medical Instruments Corp.
Iur Reciprocating Morcellator Model # 7210517	Smith & Nephew Inc.
Truclear Morcellation System And Truclear Morcellators	Smith & Nephew Inc.
Truclear Morcellator System	Smith & Nephew Inc.
Trokamed Morcellator	Trokamed Gmbh
LiNA Xcise	LiNAMED
Ablative Devices	
ExAblate 2000	General Electric Medical Systems
VizAblate (not FDA-approved for use in the U.S.)	Gynesonics
Acessa	Halt Medical
Thermachoice Thermal Balloon Ablation system	Gynecare, Inc
NovaSure Impedance Controlled Endometrial Ablation System	Hologic Corporation; Cytyc Corporation
Her Option	American Medical Systems, Inc
Hydro ThermAblator System	Boston Scientific Corporation
Microwave ablation	Microsulis
Artery Occlusion	
Doppler-Guided Uterine Artery Occlusion (DUAO) Device (Gynecare Gynocclude D-UAO)	Ethicon
Microspheres for Embolization	
Embosphere®	Merit Medical Systems
Hysteroscopic and/or Laparoscopic	
da Vinci Surgical System	Intuitive Surgical
MyoSure Hysteroscopic Tissue Removal System (Hysteroscopic)	Hologic

Table A-3. Preliminary PubMed search strategy

Terms		Results
#1	((leiomyoma[mh]) OR (fibroma[mh] AND (uterine diseases[mh] OR uterus[mh])))	17559
#2	(Uterine[tiab] AND (fibroma*[tiab] OR fibroid*[tiab] OR leiomyoma*[tiab] OR myoma*[tiab] OR fibromyoma*[tiab])) OR (submucous fibroid*[tiab] OR submucosal fibroid*[tiab] OR Intramural fibroids [tiab]) NOT medline[sb]	964
#3	#1 OR #2	18503
#4	((((((("Mifepristone"[Mesh] OR "ulipristal"[Supplementary Concept]) OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh]) OR "Antifibrinolytic Agents"[Mesh]) OR "Goserelin"[Mesh]) OR "cetrorelix"[Supplementary Concept]) OR "Selective Estrogen Receptor Modulators"[Mesh]) OR "Levonorgestrel"[Mesh]	85952
#5	therapy[sh:noexp] OR drug therapy[mh] OR drug therapy[sh] OR complementary therapies[mh] OR Treatment outcome[mh]	4541911
#6	(Mifepristone[tiab] OR Ulipristal acetate[tiab] OR NSAID[tiab] OR antifibrinolytic[tiab] OR Goserelin[tiab] OR cetrorelix acetate[tiab] OR Selective estrogen receptor modulators[tiab] OR SERM[tiab] OR mirena[tiab] OR Ing-ius[tiab] OR levonorgestrel-releasing intrauterine system[tiab]) NOT medline[sb]	1474
#7	#4 OR #5 OR #6	4578967
#8	surgery[sh] OR surgical procedures, operative[mh] OR embolization, therapeutic[mh]	3041828
#9	(Hysterectomy[tiab] OR myomectomy[tiab] OR emboliz*[tiab] OR ablation[tiab] OR ultrasound[tiab] OR uterine artery occlusion[tiab] OR Uterine artery embolization[tiab] OR UAE[tiab]) NOT medline[sb]	31999
#10	#8 OR #9	3073791
#11	#3 AND #7	3830
#12	#3 AND #10	8878
#13	#11 OR #12	10114

Notes: "Drug therapy"[mh] includes hormone therapy; "Surgical procedures, operative"[mh] includes ultrasound ablation, embolization, and hysterectomy

Table A-4. Preliminary search strategy for harms of morcellation (PubMed)

	Query	Results
#1	morcellation	445
#2	morcellat* AND uterine	256
#3	morcellat*	562
#4	("Electrosurgery/adverse effects"[Mesh]) OR "Uterine Myomectomy/adverse effects"[MeSH] OR morcellat*	1251
#5	("Electrosurgery/adverse effects"[Mesh] AND uterine) OR "Uterine Myomectomy/adverse effects"[MeSH] OR morcellat*	737

Table A-5. Agency web sites

AGENCY	WEBSITE
American College of Obstetricians and Gynecologists	http://www.acog.org/
American Association of Gynecologic Laparoscopists	https://www.aagl.org/
Society of Interventional Radiologists	http://www.sirweb.org/
Society of Gynecologic Surgeons	http://www.sgsonline.org/
American Institute for Ultrasound in Medicine	http://www.aium.org/
Food and Drug Administration	http://www.fda.gov/
European Medicines Agency	http://www.ema.europa.eu/ema/
National Health Service / National Institute for Health and Care Excellence	https://www.nice.org.uk/
HealthCanada	http://www.hc-sc.gc.ca/index-eng.php