Effective Health Care Program
Research Reports

Number 31

Identification of Future Research Needs in the Comparative Management of Uterine Fibroid Disease

A Report on the Priority-Setting Process, Preliminary Data Analysis, and Research Plan

Richard E. Gliklich, M.D.
Michelle B. Leavy, M.P.H.
Pricilla Velentgas, Ph.D.
Daniel M. Campion, M.B.A.
Penny Mohr, M.A.
Raj Sabharwal, M.P.H.
Danielle Whicher, M.H.S.
Evan R. Myers, M.D., M.P.H.
Wanda K. Nicholson, M.D., M.P.H., M.B.A.

Research from the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

March 2011

The DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) network is part of AHRQ's Effective Health Care Program. It is a collaborative network of research centers that support the rapid development of new scientific information and analytic tools. The DEcIDE network assists health care providers, patients, and policymakers seeking unbiased information about the outcomes, clinical effectiveness, safety, and appropriateness of health care items and services, particularly prescription medications and medical devices.

This report is based on research conducted by the Outcome DEcIDE Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2005-0035-I). The AHRQ Task Order Officer for this project was Shilpa H. Amin, M.D., M.B.Sc., FAAFP. The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or the U.S. Department of Health and Human Services.

None of the investigators has any affiliations or financial involvement that conflicts with the materials presented in this report.

Acknowledgements:
The investigators kindly acknowledge: Shilpa H. Amin, Elise Berliner, Parivash Nourjah, Scott Smith, Yen-Pin Chiang, Jean Slutsky, and the AHRQ Effective Healthcare Program staff for their academic guidance, scientific contributions, and administrative support on this project.

Suggested citation:
Gliklich RE, Leavy MB, Velentgas P, Campion DM, Mohr P, Sabharwal R, Whicher D, Myers ER, Nicholson WK. Identification of Future Research Needs in the Comparative Management of Uterine Fibroid Disease. A Report on the Priority-Setting Process, Preliminary Data Analysis, and Research Plan. Effective Healthcare Research Report No. 31. (Prepared by the Outcome DEcIDE Center, under Contract No. HHSA 290-2005-0035-I, TO5). AHRQ Publication No. 11-EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. Available at: http://effectivehealthcare.ahrq.gov/reports/final.cfm.

Contents

Tables

Figure

Appendixes

Author affiliations:
Richard E. Gliklich, M.D.[1]
Michelle B. Leavy, M.P.H.[1]
Priscilla Velentgas, Ph.D.[1]
Daniel M. Campion, M.B.A.[1]
Penny Mohr, M.A.[2]
Raj Sabharwal, M.P.H.[2]
Danielle Whicher, M.H.S.[2]
Evan R. Myers, M.D., M.P.H.[3]
Wanda K. Nicholson, M.D., M.P.H., M.B.A.[4]

[1]Outcome DEcIDE Center
[2]Center for Medical Technology Policy
[3]Duke University
[4]University of North Carolina

Executive Summary

In 2003, the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) was signed into law. Section 1013 of MMA authorized the Agency for Healthcare Research and Quality (AHRQ) to conduct and support research on comparative effectiveness and clinical effectiveness, and to disseminate the findings of that research to stakeholders. AHRQ organized the Effective Health Care (EHC) Program to meet the requirements of Section 1013. The legislation also required that the needs of Medicare, Medicaid, and the Children's Health Insurance Program drive AHRQ's research priorities. The primary goals of Section 1013 are to develop valid scientific evidence about the comparative effectiveness of different treatments and appropriate clinical approaches to difficult health care problems and to make this information easily accessible to decisionmakers. The conduct of new research in areas where existing scientific evidence is insufficient to inform health care decisions is an important step to meet the goals of Section 1013. As part of the EHC program and Section 1013 of MMA, the AHRQ Effective Healthcare , DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Program developed an evidence 'generation' focused task order designed to revisit the current state of evidence-based research gaps in a priority population condition area of gynecological health as identified in prior AHRQ evidence based-practice center systematic reviews. AHRQ has funded this project to develop a prioritized research agenda and protocol to study the clinical and/or comparative effectiveness of uterine fibroid disease diagnosis, management, care coordination, and treatment.

Uterine fibroids (leiomyomata) are the most common noncancerous tumors in women of childbearing age and the second most common reason women of reproductive age undergo surgery. Uterine fibroids, which result in more than 200,000 hysterectomies every year, have no known cause and limited treatment options. In the United States it is estimated that approximately 1 percent of women with employer-provided insurance have clinically significant uterine fibroids, and the direct costs associated with treating uterine fibroids are more than $1 billion annually. Treatment options for symptomatic uterine fibroids include watchful waiting; nonprocedural treatments (medical therapies) such as hormonal therapies, oral contraceptives, and nonsteroidal anti-inflammatory drugs; and a number of procedural treatments ranging from surgical or incisional such as hysterectomy or myomectomy, to nonsurgical (also called nonincisional or minimally invasive) such as uterine artery embolization and magnetic resonance image-guided focused ultrasound.

Despite the prevalence and possible complications of uterine fibroids, few published studies examining the effectiveness of treatment strategies exist. Little information is available on the long-term effects of procedural or medical therapy on fibroid disease symptoms, recurrence, and patient-reported outcomes. The currently available literature is insufficient to draw conclusions about the relative benefits, harms, or costs of the available choices, making it difficult for decisionmakers (e.g., patients, providers, payers, and others) to select appropriate treatments. New research is needed to address the questions facing decisionmakers. Additionally, a new collaborative model for developing a research plan is needed to ensure that the research meets the needs of decisionmakers. As recommended by the Institute of Medicine (IOM) in its report on comparative effectiveness research, this model should incorporate the perspectives of health care decisionmakers in the strategic planning, priority setting, and research plan development. (See Crossing the Quality Chasm, 2000, available at:

http://www.iom.edu/Global/News%20Announcements/Crossing-the-Quality-Chasm-The-IOM-Health-Care-Quality-Initiative.aspx.)

The goals of the project are (1) to develop a consultative partnership with multiple stakeholders to identify clinical problems for which new research will inform treatment decisions for patients and providers (especially beneficiaries of the Medicare and Medicaid programs); (2) to identify, in partnership with stakeholders, clinically or policy-relevant research questions related to the clinical and/or comparative effectiveness of uterine fibroid treatment and management; (3) to design in partnership with stakeholders, researchers, and AHRQ a research protocol for a multicenter prospective study of the comparative effectiveness of diagnosis, management, care coordination, and/or treatment of uterine fibroids; (4) to conduct a preliminary analysis of existing data to inform the protocol development and assess the prioritized research questions identified by stakeholders; and (5) to disseminate, in collaboration with AHRQ, the findings of the project to stakeholder partners and other stakeholder groups.

The Outcome DEcIDE Center has conducted this project for and in collaboration with the AHRQ Effective Healthcare DEcIDE Program and with several individuals and organizations with particular areas of expertise. Drs. Evan Myers of Duke University and Wanda Nicholson of the University of North Carolina at Chapel Hill provided key clinical and epidemiological expertise and cochaired the Technical Working Group (TWG). The Center for Medical Technology Policy (CMTP) provided special expertise and leadership in stakeholder engagement and research prioritization; and JEN Associates performed background analyses on the data sets.

The purpose of this paper is to provide an interim report on the first three objectives of the project and outline the next steps for achieving the fourth objective. This paper is divided into three sections. The first section describes the processes used to engage stakeholders in a collaborative partnership and develop a stakeholder-driven research agenda. The second section presents the stakeholder-driven research agenda. The final section discusses the next steps in the project, including the creation of a research protocol and the use of data analyses to support the protocol development.

The stakeholder engagement and priority-setting phases of the project focused on developing a consultative partnership among multiple stakeholders, identifying key evidence gaps, and prioritizing research questions related to the treatment and management of uterine fibroids. As part of the stakeholder recruitment and engagement process, AHRQ provided guidance to the project team to strive to include a broad spectrum of stakeholders representing patients; consumers; biomedical, clinical translational science investigators; health plans; academic scientists; clinicians; industry; policy makers and state and federal partners all relevant and interested in advancing comparative uterine fibroid disease research. Having potential partners with the capability to disseminate research findings or to integrate directly into decision making and future research and translational activities was a core consideration. The project team, in consultation with the AHRQ EHC DEcIDE program staff, assembled two distinct but interrelated stakeholder groups for these tasks: Technical Working Group (TWG) subcommittee to provide technical expertise and prepare for the priority-setting meeting (eight members), and a diverse 34 member Stakeholder Committee for priority setting.

The primary goal of the TWG was to narrow the list of evidence gaps identified from systematic reviews to a manageable number to present to the Stakeholder Committee. The TWG also assisted the project team in translating the evidence gaps into research questions, identifying current or planned studies that might affect the relative importance of a specific question, and developing appropriate background materials for the Stakeholder Committee. The primary

objective of the Stakeholder Committee was to identify the highest priority research questions for uterine fibroid disease treatment and management. The Committee also provided information on issues to consider in developing the research protocol.

The priority-setting process began with the TWG. The TWG reviewed the initial list of questions and scored each question using priority-setting criteria developed by the project team. Next, the TWG met to discuss, refine, and revise the questions. After the meeting, the TWG rescored the questions. The two prior AHRQ Evidence Reports informed the TWG's discussions and rankings.[1,2] Using the data from the second scoring, the project team assembled a list of the top 12 research questions. The team developed general and question-specific background materials and distributed them to the Stakeholder Committee. Next, the Stakeholder Committee met to discuss and prioritize the list of 12 research questions. This meeting produced a final prioritized research agenda for uterine fibroid disease management and treatment.

The next step in the project was to develop a study protocol to address the highest priority research questions. To develop the protocol, the project team assessed study design options, defined the study objectives, determined the setting and participants, designed the data collection plan, and developed the statistical analysis plan. In selecting a study design option, the project team considered difficulties with randomization raised during the Stakeholder Committee meeting. The team also reviewed the findings from the preliminary data analyses conducted for this project. The data analyses produced descriptive profiles of patient populations with a uterine fibroid diagnosis, using data from the National Inpatient Sample, the State Ambulatory Surgery database, and the Medicaid program. While the data analyses provided valuable insights into variation in treatment patterns, they also highlighted the limitations of retrospective claims-based data analyses, including an inability to adjust data to reflect disease severity or other potential confounders and difficulty in determining initial treatment choices. Due to these factors, the study is planned as a prospective, observational cohort study that will not provide or recommend any treatment.

The prospective, observational study design offers several potential benefits, as well as some limitations. First, the observational nature of the design will allow the study to have broad inclusion criteria and minimal exclusion criteria. The study will also enroll patients from a diverse group of study sites, with the goal of producing results generalizable to a wide range of uterine fibroid disease patients who present to a variety of practice settings nationwide. By leaving treatment decisions up to the patient and provider (and not randomizing patients to a particular treatment protocol), the study may include a larger percentage of eligible patients. Unlike retrospective studies, which are limited by the availability of existing data, the prospective design will allow the study to collect detailed clinical data, as well as patient-reported outcomes. The study design also allows for long-term (5-year) followup with patients. Limitations of the study may include confounding by indication. However, efforts will be made to measure all known predictors of treatment decision and response to therapy and to include key predictive variables in multivariate analysis to minimize the effects of confounding by indication.

The objectives of the planned study are: (1) to evaluate the effectiveness of different treatment pathways in achieving relief from symptoms of uterine fibroids and overall quality of life, with a focus on (a) comparison of hysterectomy as first procedural treatment to uterus-sparing procedural treatments, and(b) comparison of all procedural treatments to nonprocedural (medical) treatments; and (2) to describe the pathways of management and treatment for symptomatic uterine fibroids of greater than 6 months' duration among women who have tried

and "failed" at least one medical treatment. The draft study protocol will be circulated to the Stakeholder Committee and revised in consultation with the Committee and AHRQ.
Two additional data sources are currently being analyzed to further refine the protocol. These data sources were derived from the Medical Quality Improvement Consortium of General Electric Healthcare and the Fallon Clinic Community Healthplan, Fallon Clinic Research. Appendix 1, Table A.2.

These data sources were selected to provide more information on patterns of care, comorbidities, and predictors of patient care for uterine fibroid disease. Both data sources are equipped to provide a clinically rich, longitudinal picture of patient care. These data sources can also further examine patient treatment by age, race, body mass index, smoking status, and other important patient-level demographic and clinical variables. One source of data is a national electronic health record (EHR) system, with data from 15 million of patients in 43 states. This representative sample of the U.S. population will provide detailed patient profiles of a large sample of women with uterine fibroid disease. The second data source, while restricted to patients in the northeastern United States, provides an integrated picture (EHR data, claims data, pharmacy data) of patient care across multiple settings, thus ensuring that a comprehensive view of patient care is provided. In selecting these data sources, the project team hopes to overcome some of the limitations of the preliminary data analyses. In particular, these data sources are intended to provide a picture of treatment patterns over time in a more representative patient population. The two primary goals of these data analyses are: (1) to provide information on treatment patterns and progression of treatments over time to assess the feasibility of the proposed study design; and (2) to examine the types of data related to uterine fibroid disease that are routinely collected, in order to understand the data collection burden of the proposed study.

This project offered a unique opportunity to involve stakeholders in setting a research agenda for the treatment and management of uterine fibroids. The stakeholders, organized into the small Technical Working Group and larger Stakeholder Committee, provided guidance on developing the initial list of 64 research questions, revising and narrowing the list to 12 questions, and prioritizing the final questions. The stakeholders included patient, consumer, clinician, insurer, and Federal agency representatives. The inclusion of multiple stakeholder groups established a balanced approach to the selection of research priorities. Through transparent interaction with a broad and inclusive Stakeholder Committee, the project attempted to overcome a major flaw in the current clinical research enterprise, where researchers may become disconnected from the practical needs of patients and clinicians. The result of this process is a prioritized research agenda that should reflect the needs of those making decisions related to the treatment and management of uterine fibroids. This paper documents the strengths and limitations of this approach to priority setting and stakeholder engagement and may help to guide similar efforts in the future.

Introduction

Project Background

In 2003, the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) was signed into law. Section 1013 of MMA authorized the Agency for Healthcare Research and Quality (AHRQ) to conduct and support comparative effectiveness and clinical effectiveness research and to disseminate the findings of that research to stakeholders. The legislation required that the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP) drive AHRQ's research priorities. The primary goals of Section 1013 are to develop valid scientific evidence about the comparative effectiveness of different treatments and appropriate clinical approaches to difficult health care problems and to make this information easily accessible to decisionmakers. The conduct of research in areas where existing scientific evidence is insufficient to inform health care decisions is an important component of Section 1013.

To meet the goals of Section 1013, AHRQ formed the Effective Health Care (EHC) Program. The program produces systematic reviews, generates new evidence and analytic tools, and compiles and translates research findings into useful formats for stakeholders. The EHC Program is made up of three groups that work collaboratively to meet its goals. The three groups are the Evidence-based Practice Centers (EPCs), the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network, and the Eisenberg Center. The EPCs are primarily responsible for synthesizing and translating evidence-based research findings to help improve the quality, effectiveness, and appropriateness of health care. The DEcIDE Network conducts studies on the outcomes, effectiveness, safety, and usefulness of medical treatments and services. The Eisenberg Center translates the reports produced by the EHC Program into user-friendly guides and tool for consumers, clinicians, and policymakers. The Scientific Resource Center also provides support for the EHC program, specifically for tasks related to communicating with stakeholders, assisting with the development of key study questions and research topics, and coordinating peer review and public input.

The activities of the EHC program produce a variety of products to support the development of new scientific knowledge to inform health care decisions. The underlying goal of the program activities is to provide decisionmakers (patients, providers, payers, and others) with the best available evidence to inform their health care decisions. In particular, the program focuses on improving the quality, effectiveness, and efficiency of public insurance programs, such as Medicare, Medicaid, and CHIP, by addressing research needs related to diseases with high burden.

As part of the EHC program and Section 1013 of MMA, AHRQ has funded this project to develop a prioritized research agenda and protocol to study the clinical and/or comparative effectiveness of uterine fibroid disease diagnosis, management, care coordination, and treatment.

Clinical Background

Uterine fibroids, also known as uterine leiomyomata, are the most common gynecological condition among women. Occurring most frequently among women ages 30 to 40, cumulative incidence approaches 70 percent among white women by age 50 and is even higher among African American women.[3,4,5] Although the tumors are benign and usually asymptomatic, they can cause pain, heavy menstrual bleeding, and anemia, and they are associated with a range

of adverse reproductive outcomes, including infertility, spontaneous abortion, preterm birth, and cesarean delivery.[6]

Treatment options for symptomatic uterine fibroids include watchful waiting, nonprocedural treatments such as hormonal therapies, oral contraceptives, and nonsteroidal anti-inflammatory drugs (NSAIDS), and a number of procedural treatments ranging from surgical or incisional treatments such as hysterectomy or myomectomy, to nonsurgical (also called nonincisional or minimally invasive) treatments such as uterine artery embolization and magnetic resonance image-guided focused ultrasound (see glossary in Appendix F). Note, for the purposes of this paper, the term "procedural" refers to procedure-based treatment strategies (including surgical and nonsurgical) while the term "nonprocedural" refers to medical treatment strategies used primarily for treatment of symptoms.

Most women who have uterine fibroids will not experience symptoms severe enough to seek treatment, but for those who do, uterine fibroid disease poses a significant cost and quality of life burden.[7,8,9] Hysterectomy and myomectomy procedures for symptomatic uterine fibroids were estimated using National Inpatient Sample (NIS) data to cost upwards of $2 billion in 1997,[10] and quality-of-life burden approaches that of other chronic diseases, with absenteeism and disability accounting for a significant component of the cost burden.[11] Uterine fibroids are the single most common indication for hysterectomy.[12] An analysis of the NIS data conducted for this project found that 187,423 abdominal hysterectomies, 46,070 laparoscopic hysterectomies, and 30,613 vaginal hysterectomies were performed in 2007 in women with a primary or secondary ICD9-CM diagnosis of uterine fibroids (see Appendix A).

While hysterectomy is the most common treatment for women with severe symptoms, its use has been declining as less invasive treatment alternatives have emerged.[13] For women of childbearing age, preservation of the uterus is a major factor driving treatment choice. Myomectomy, which removes the fibroids while leaving the uterus intact, is an alternative to hysterectomy. The NIS data analysis found that 39,028 myomectomies were performed in 2007. Significant geographic variation in treatment patterns exists, however. Analyses of the State Inpatient Database and the State Ambulatory Surgery Database for five states (California, Florida, Maryland, New York, and Wisconsin) found that the rate of abdominal hysterectomy was lowest in Maryland (22 percent) and highest in California (32 percent). The rates of nonabdominal hysterectomy also varied between states. For example, the rates of laparoscopic hysterectomy and myomectomy were 7 percent and 18 percent, respectively, in New York. In comparison, the rates for the same two procedures were 17 percent and 8 percent, respectively, in Wisconsin. The reasons for the geographic variation in treatment patterns are unclear and may merit further research.

Alternative procedures, such as uterine artery embolization (UAE) and magnetic resonance image-guided focused ultrasound (MRgFUS), are also available. However, little is known about the long-term benefits and risks of any of the available procedures.[14] Short-term medical treatment with hormonal therapy such as gonadotropin-releasing hormone (GnRH) agonists is effective for reducing fibroid size prior to surgery and for reducing menstrual blood loss to provide temporary symptom relief. The adverse effects of hypoestrogenism limit their utility as long-term treatments, though.[15] Complementary and alternative methods such as herbal preparations have also been used but data on their effectiveness are not available.[16]

Despite the prominence of uterine fibroids as a concern for women's health, little is known about many aspects of the condition, including the etiology of the disease, the natural history of fibroids, the impact of fibroids on fertility, and the impact of treatment on reproductive

outcomes. Virtually no well-designed long-term epidemiological studies exist in this disease area. The evidence on the comparative long-term effectiveness of treatment options is also of poor quality. The authors of a 2007 technology assessment prepared for AHRQ on the management of uterine fibroids noted a specific lack of "well conducted trials in U.S. populations that directly compared treatment options…"[17] They concluded that "research to assess how patient characteristics influence outcomes is meager. The current state of the literature does not permit definitive conclusions about benefit, harm, or relative costs to help guide women's choices." These findings mirror the conclusions of an earlier AHRQ-sponsored assessment completed by Myers et al.[18] The authors of a 2001 assessment laid out a detailed list of questions for future research. Recent review of the clinical research literature on uterine fibroid practice patterns between 2001 and 2007 showed continual gaps in uterine fibroid research to address provider-patient decision-making and treatment selections. Two systematic reviews completed since the 2007 technology assessment arrived at similar conclusions.[19,20]

Several factors contribute to the lack of evidence to support treatment choices for uterine fibroids. First, adequately sized randomized trials with long-term followup, especially for surgical procedures such as hysterectomies, are rare. Historically, both women and physicians have been reluctant to participate in trials where hysterectomy is one of the potential treatments.[21,22] Second, the utility of administrative and claims databases is limited in this disease area. The population most affected by the disease is not typically covered by Medicare. Medicaid data may include some patients, but these patients are not generalizable to the broader patient population. Medicaid also does not cover many of the treatment alternatives to hysterectomy, which limits the usefulness of the data. Patients in the age group affected by uterine fibroids may be more mobile occupationally and geographically, limiting the potential ability of private payer data to provide long-term outcomes. Routine hospital discharge data do not capture many of the important patient characteristics that determine short-term outcomes such as complications.[23]

In addition to these issues, many of the characteristics of the condition contribute to difficulties in designing research that could be used to inform treatment choices. Uterine fibroids cause a range of symptoms, and a treatment that is effective in relieving one type of symptom (e.g., bleeding) may be less effective at relieving other symptoms (e.g., pelvic pressure). Many of the demographic characteristics more common among women with fibroids (later reproductive age, African American race) are also risk factors for adverse reproductive outcomes such as preterm birth, confounding the potential association between uterine fibroids and these outcomes.[24] Finally, even large studies may have insufficient power to generate useful estimates for important but relatively rare outcomes. For example, the effect of conservative uterine fibroid treatment on pregnancy outcomes is of great clinical interest. However, powering a single study to generate estimates of event rates may be difficult for two reasons: (1) women with fibroids are likely to have lower pregnancy rates because of their age (even if the fibroids have no effect on fecundity); and (2) adverse pregnancy rates are relatively rare.

The failure of clinical research to target the main questions of concern to decisionmakers (e.g., patients, providers, payers, and others) is not unique to uterine fibroid treatment. Traditionally, a disconnect has existed between the output of the clinical research enterprise, which generates studies for regulatory approval or to reflect the academic interests of clinical and health services researchers, and the needs of patients and their clinicians for determining the appropriate course of treatment.[25] Systematic reviews of the medical literature commonly conclude that there is no reliable evidence supporting the use of the medical technology in

question and recommend further research. This disconnect between decisionmakers' needs and the available clinical research has been a major impetus behind the recent increase in funding for comparative effectiveness research (CER). CER is not clinical research as usual. Instead, it is an attempt to reshape the clinical research enterprise to produce information that will be relevant to decisionmakers, including consumers. The Institute of Medicine (IOM) Committee on Comparative Effectiveness Research Prioritization underscored this point, stating, "The CER Program should fully involve consumers, patients, and caregivers in key aspects of CER, including strategic planning, priority-setting, research proposal development, peer review, and dissemination."[26]

Rationale

Despite the prevalence and possible complications of uterine fibroids, there are a limited number of published outcomes studies examining the effectiveness of existing therapies. The currently available literature is insufficient to draw conclusions about the relative benefits, harms, or costs of the available choices, making it difficult for decisionmakers to select appropriate treatments. New research is needed to address the questions facing decisionmakers. This research will also help to address several of the IOM's 100 initial priority topics for comparative effectiveness research that relate to improving pregnancy outcomes and preventing pre-term birth.

Additionally, a new collaborative model for developing a research plan is needed to ensure that CER meets the needs of decisionmakers. As recommended by the IOM, this model should incorporate the perspectives of health care decisionmakers in the strategic planning, priority setting, and research plan development.

Objectives

The goal of this project is to engage stakeholders in a collaborative process to develop a comprehensive research plan for uterine fibroid disease. The five objectives of this project are to:

1. Form a collaborative partnership with a broad group of stakeholders in the area of management of uterine fibroid disease, spanning patients and consumer organizations, clinicians and professional societies, experts in basic, clinical, and translational research, health payers, product developers, and policymakers.
2. In concert with this stakeholder group, identify and prioritize a set of research questions related to the burden of uterine fibroid disease, its etiology, the natural history of fibroid development and outcomes, and the comparative effectiveness of available treatment options for uterine fibroids, concluding with a white paper describing the stakeholder-driven research agenda and the process used to develop it.
3. Conduct preliminary data analysis to inform the development of a protocol to evaluate key research questions.
4. Work with the stakeholder group to develop a multicenter research protocol and analysis plan to address the top priority research questions, considering various methodological approaches.
5. Actively participate in dissemination of the research agenda as well as the results of the preliminary data analysis, and in activities related to translation to stakeholder groups.

The Outcome DEcIDE Center has conducted this project for and in collaboration with AHRQ with several individuals and organizations with particular areas of expertise. The

Outcome DEcIDE formed a project team that included two clinical experts, Dr. Evan Myers of Duke University and Dr. Wanda Nicholson of the University of North Carolina at Chapel Hill, the Center for Medical Technology Policy (CMTP), and JEN Associates. Drs. Myers and Nicholson provided key clinical and epidemiological expertise. CMTP provided special expertise and leadership in stakeholder engagement and research prioritization. JEN Associates performed the preliminary data analyses on the National Inpatient Sample, the State Ambulatory Surgery database, and the Medicaid program dataset described above and in Appendix A.

The purpose of this paper is to provide an interim report on the first three objectives and outline the next steps for achieving the fourth objective. This paper is divided into three sections. The first section describes the processes used to engage stakeholders in a collaborative partnership and develop a stakeholder-driven research agenda. The second section presents the stakeholder-driven research agenda. The final section discusses the next steps in the project, including the creation of a research protocol and the use of data analyses to support the protocol development.

Stakeholder Engagement and Priority Setting

The stakeholder engagement and priority-setting phases of the project focused on developing a consultative partnership among multiple stakeholders, identifying key evidence gaps, and prioritizing research questions related to the treatment and management of uterine fibroids.

Stakeholder Engagement

This project offered a unique opportunity to involve stakeholders in setting a research agenda for the treatment and management of uterine fibroids. Based on CMTP's past experience with priority setting and convening workgroups,[27] the project team assembled two distinct but interrelated working groups: a TWG subcommittee to provide technical expertise and prepare for the priority-setting meeting (eight members), and a diverse 34-member Stakeholder Committee for priority-setting. All members of the TWG were also members of the Stakeholder Committee. Two members of the project team, Dr. Myers and Dr. Nicholson, served as the cochairs of the TWG and on the Steering Committee. The activities and deliberations of the TWG and Stakeholder Committee were designed to ensure a comprehensive identification of knowledge gaps related to the management and treatment of uterine fibroids, facilitate discussion and deliberations to select the highest priority research questions, and inform the subsequent protocol development. These groups are described further below.

Technical Working Group

The TWG had five objectives:

1. Narrow the list of evidence gaps identified from systematic reviews to a manageable number to present to the Stakeholder Committee;
2. Assist the team in translating the evidence gaps into research questions;
3. Identify current or planned studies that might affect the relative importance of a specific question;
4. Provide input on potential study designs, feasibility, or operational issues associated with the highest priority questions; and
5. Provide specific content knowledge for the Stakeholder Committee.

To fulfill this role, the project team organized a small TWG made up of clinician researchers, payers, and patient/consumer representatives. The translation of evidence gaps into research questions is a critical step in the priority-setting process, as research questions need to be specific and clear to allow for effective priority setting and subsequent research design. Compounded research questions that mention multiple patient groups, interventions, or outcomes inhibit priority-setting exercises.[28] The development of the questions requires in-depth knowledge of the field. Based on previous experience, the team included a majority of clinician researchers with experience in treating uterine fibroids, planning and implementing studies in the disease area, or completing technology assessments or systematic reviews in the disease area. Clinician researchers tend to be knowledgeable about new developments in treatments and understand current treatment patterns. They also have the necessary research experience to translate evidence gaps into research questions.

Other decisionmakers bring different perspectives and opinions. Payers help to ensure that the research questions include aspects of care and outcomes that are relevant to third-party payers. Payers also review evidence from a population perspective, which gives them insight into evidence gaps that affect large numbers of patients (vs. the more individualized patient/clinician perspective). Finally, payers provide unique information on the treatments for which patients are demanding coverage and why.

Including patient and/or consumer group representatives in the TWG is also important. One of the project team members (CMTP) regularly convenes a Patient Consumer Advisory Committee (PCAC) to provide meaningful and substantive input on the organization's activity from the perspective of patients and consumers. The PCAC, a six-member committee that includes leadership from national patient and consumer advocacy organizations, such as the National Partnership for Women and the Center for Advancing Health, has noted that patients feel more empowered to provide their opinions and insight when more than one patient representative is in the group. This advice stems from members' own experience and from advocates trained by their respective organizations. Patient and consumer representatives can provide valuable insights into the choices facing patients, the effects of the treatments and the disease on quality of life, and the types of missing information that would be useful to patients. For this project, the project team's intent was to identify representatives for the TWG with specific knowledge of the disease but no clear bias with regard to the therapeutic options.

The TWG for this project was made up of five clinicians with experience in uterine fibroid disease research, a payer representative involved in a pilot study for his health plan on the relative effectiveness of UAE, and two patient/consumer representatives with in-depth knowledge of the disease and the available treatment options. The project team's clinical experts, Drs. Myers and Nicholson, helped to identify clinical experts for the TWG and chaired the group. AHRQ staff also provided recommendations based on their prior work in this disease area. Notably, the TWG included two authors from the AHRQ-funded technology assessments on the management of uterine fibroid disease.[29,30] A list of the TWG members and their affiliations is provided in Appendix B.

Stakeholder Committee

The primary objective of the Stakeholder Committee was to identify the highest priority research questions for uterine fibroid disease treatment and management. The Committee also provided information on potential issues to consider in developing the research protocol. To ensure a broad range of perspectives, the project team recruited clinician researchers, public and private payers, employers, patient and consumer group representatives (including patients with diverse uterine fibroid disease perspectives: treated, recurrent treatment and untreated), Federal agency representatives, and product developer representatives. Many of the clinician researchers also represented professional societies, such as the American College of Obstetrics and Gynecology, the American Society for Reproductive Medicine, and the Society for Interventional Radiology. The Federal agencies represented on the Stakeholder Committee included the Office of Women's Health at the Food and Drug Administration; the National Center for Complementary and Alternative Medicine; the Office of Research on Women's Health at the National Institutes of Health; and the Division of Reproductive Health at the Centers for Disease Control and Prevention. While industry representatives were not included in the TWG, there were individuals with industry affiliations in the Stakeholder committee because of their considerable knowledge in designing and executing clinical studies in the fibroid disease

area, their in-depth understanding of current and emerging treatments, and their market perspectives. There were no direct industry representatives selected for the Technical Workgroup. A consumer representative for the Uterine Fibroid Foundation was also a representative for the Focus Ultrasound Surgery Foundation and was included in the technical working group and stakeholder discussions.

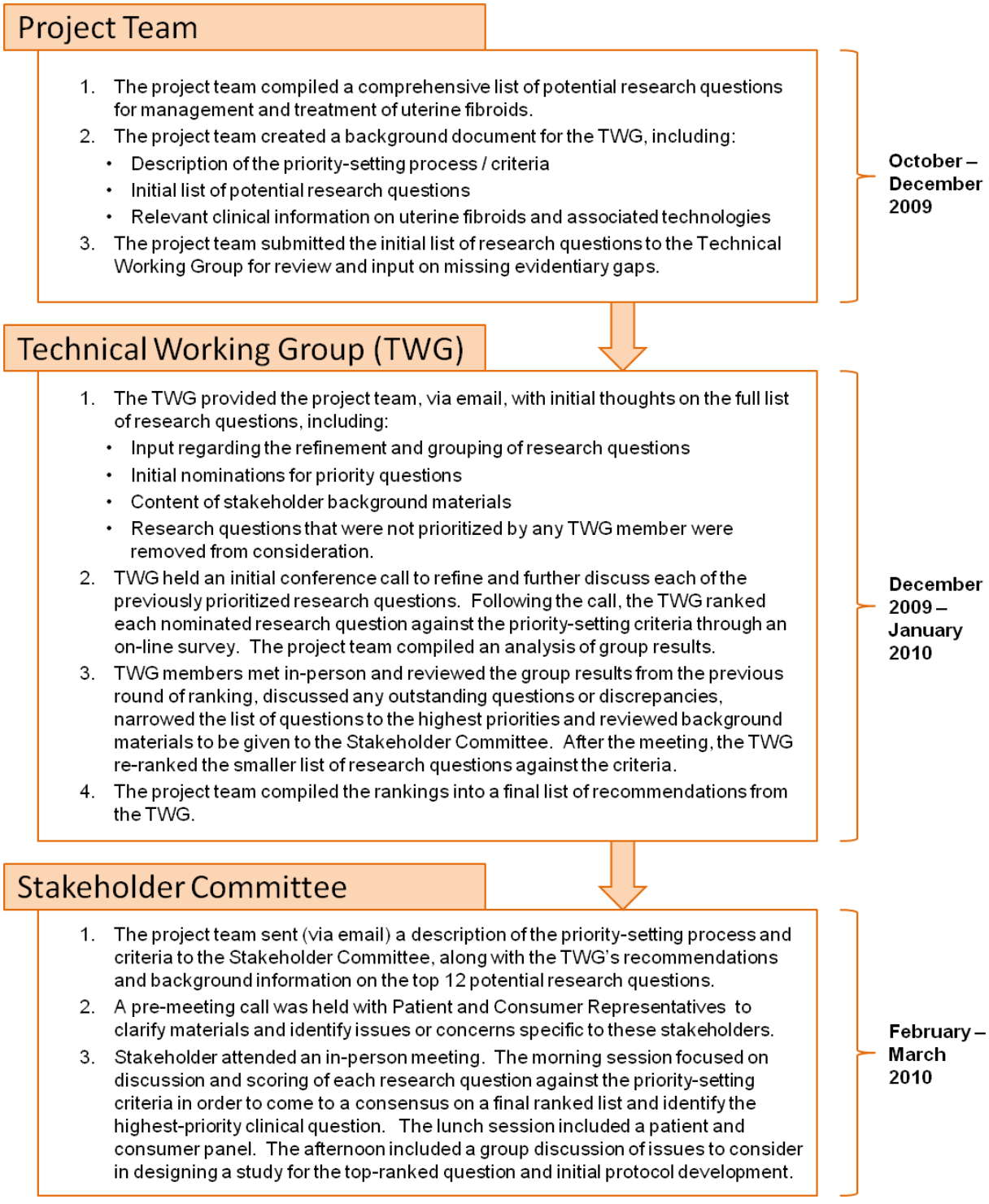
The project team sought to include authors of seminal papers on treatment and management of uterine fibroids, clinical experts from manufacturers of commonly used treatments, and stakeholders who had participated in other Federal initiatives in this disease area. The team relied on reviews of the literature, Internet searches, and recommendations from the TWG and AHRQ staff. All members of the TWG were included in the Stakeholder Committee to ensure continuity in the process. A list of the Stakeholder Committee members and their affiliations is provided in Appendix C.

The inclusion of multiple stakeholder groups established a balanced approach to the selection of research priorities. Through transparent interaction with a broad and inclusive Stakeholder Committee, the project overcomes a major flaw in the current clinical research enterprise, where researchers may become disconnected from the practical needs of patients and clinicians.

Priority-Setting Process

The project team used a modified Delphi approach for the priority-setting process. The three primary elements of the modified Delphi approach are (1) using anonymous surveys to gather viewpoints; (2) gathering feedback using successive questionnaires, to allow participants to reconsider their views after discussion of the group views; and (3) using a panel of experts to guide the process.[31,32] The priority-setting process for this project involved three major steps. First, the project team identified evidence gaps and developed a list of potential research questions. Next, the team worked with the TWG to revise and narrow the list. Lastly, the Stakeholder Committee reviewed and prioritized the refined list. An overview of the priority-setting process is provided in Figure 1. This section describes each of the steps in the priority-setting process.

Figure 1. Priority-setting process



Identification of Evidence Gaps and Development of Research Questions

The project team began the priority-setting process by compiling a comprehensive list of evidence gaps related to the management and treatment of uterine fibroids. As a comprehensive search of the primary literature to update the previous systematic reviews was not within the scope of the project, the team leveraged AHRQ's already substantial investment in summarizing the state of evidence. The 2001 AHRQ Evidence Report, *Management of Uterine Fibroids, and the 2007 AHRQ Evidence Report, Management of Uterine Fibroids: An Update of the Evidence*, were starting points.[33,34] The 2001 assessment found that the overall quality of the literature on the management of fibroids was poor, with almost no evidence to support the effectiveness of commonly recommended therapies, and the 2007 report confirmed this finding. The project team also incorporated information from the two recently completed Cochrane Collaboration reviews on herbal preparations, and on the use of Danazol, for treatment of uterine fibroids.[35,36]

The TWG members helped the project team identify recently completed studies or studies in progress that would fill some of the gaps identified in systematic reviews. Newer studies included the HOPEFUL trial, a multicenter retrospective study comparing complications from UAE and hysterectomy, and the FIBROID Registry, a multicenter prospective longitudinal study of the short- and long-term outcomes of UAE. These studies provided data on patient-reported outcome (PRO) measures for uterine fibroids and explored the costs of uterine fibroids and the cost effectiveness of interventions.[37,38,39,40] The team also sent the initial list of research questions to the Stakeholder Committee to identify any additional evidence gaps.

The evidence gaps identified through this process were varied and included the incidence and prevalence of the disease, its natural history, variation in treatment patterns by race, age, and demographic characteristics, factors influencing the most appropriate choice and timing of treatments, and methods for measuring treatment outcomes within clinical studies. The initial list of 64 research questions is provided in Appendix D.

While identifying evidence gaps, the project team also developed the priority-setting criteria (Table 1). The project team adapted the criteria from several sources, including AHRQ's Effective Health Care Program criteria for the selection and refinement of topics for comparative effectiveness reviews, the Federal Coordinating Council of Comparative Effectiveness Research prioritization criteria, and priority-setting criteria previously developed by the CMTP.[41,42,43] Members of the TWG and Stakeholder Committee were asked to use these criteria as they considered the appropriate priority for each research question.

Table 1. Priority-setting criteria

Disease burden	The proposed research will reduce disease burden (disability, morbidity, or mortality) on afflicted individuals and their families, caretakers, and communities.
Priority populations	The proposed research will target a priority population, including diverse populations and vulnerable subpopulations, with the potential to reduce inequalities in care.
Potential impact	The proposed research has potential to provide clinically significant improvement in net health outcomes and/or patient care; it addresses issues regarding both clinical benefits and potential clinical harms, including patient safety.
Variation in care	The proposed research will reduce unexplained variations (overuse, underuse, misuse) in prevention, diagnosis, access, and/or treatment protocols.
Economic impact	The proposed research has potential to lead to substantial cost efficiencies or cost savings for patients, health plans, or public health programs, through reduction of unnecessary or excessive costs.
Current body of evidence	The proposed research will fill substantial gaps in the current body of evidence—and there is no other research planned or in progress that will answer the research question—thereby contributing to reduced clinical uncertainties, changes in use and/or coverage of a technology or set of technologies (i.e., improvability of evidence or value of information).
Operational feasibility	The proposed research is operationally feasible: tentative study designs can be identified, the proposed research would be affordable and not overly burdensome upon stakeholders, and the topic is timely, especially in relation to fast-evolving technologies.
Potential for multiplicative effect	The proposed research lays a foundation or can serve as a template, for future comparative research on related research questions, data infrastructure, and/or methods development.
Appropriateness	The proposed research involves a health care drug, intervention, device, or technology available (or soon to be available) in the United States, and is relevant to Section 1013 enrollees (Medicare, Medicaid, CHIP, other Federal health care programs).

Technical Working Group: Revision and Refinement of Research Questions

Initial Scoring

The primary objective of the TWG was to narrow and refine the initial list of 64 research questions into a manageable list to present to the Stakeholder Committee. The process began with an initial rating of the research questions. The TWG members used an online scoring tool to rate each question on a scale of 0 to 10, with 0 representing the lowest priority and 10 representing the highest priority. Members also had the ability to provide comments, such as suggestions to clarify questions or concerns about the feasibility of addressing the question. The online scoring tool was selected because it enabled TWG members to complete the scoring at their convenience in an efficient manner. The scoring tool also provided the project team electronic tabulations of the ratings, which facilitated the development of summary materials for the TWG in-person meeting.

The project team then averaged the ratings for each question. Average ratings across the 64 questions ranged from a high of 9.4 to a low of 2.7. The 15 highest rated research questions all received an average score above 7.0. The 10 highest rated questions were clustered among three general categories: comparative effectiveness of treatments (procedural and nonprocedural treatments) for the management of uterine fibroids, the development of a common classification system for fibroids, and the utility of genetic markers. Other highly rated questions focused on the incidence and prevalence of uterine fibroids, measurement instruments such as patient-reported outcomes, the durability of uterine-sparing interventions, and the cost effectiveness of alternative strategies.

The average rating, mean rating, range, and average deviation from the mean for each of the questions were provided to the TWG members in advance of the in-person meeting. In addition, the project team compiled a summary of the comments from the TWG members for the top 15 questions.

In-Person Meeting of the Technical Working Group

The purpose of the in-person meeting of the TWG was to discuss the top rated questions and to determine how best to present the research questions to the Stakeholder Committee. Early in the discussion, the TWG determined that separating the questions solely by childbearing aim created unnecessary duplication. The group suggested instead that childbearing aim would be an important subpopulation to define in future research. The group then focused on developing a refined list of research questions across six categories: relative effectiveness, patterns of use, methods, natural history, genetics, and care coordination and shared decisionmaking. Highlights of the discussion around each category are provided below.

Relative Effectiveness

In the TWG's initial scoring, the majority of the highly rated research questions focused on the relative effectiveness of specific procedural or nonprocedural treatments. Given the potential for redundancies among these questions, the TWG elected to develop one broad relative effectiveness question and ask the Stakeholder Committee to recommend the specific treatment options to compare. The TWG also recommended consulting the Stakeholder Committee to identify priority subpopulations, such as women seeking to preserve their fertility or racial/ethnic groups. In addition, the group noted the importance of prioritizing the specific outcomes to measure when determining the relative effectiveness of treatments. By allowing for subquestions under the broad relative effectiveness question, the Stakeholder Committee could specify the highest priority interventions, outcomes, and subpopulations.

Patterns of Use

The TWG acknowledged that key gaps exist in the current understanding of which treatments or treatment strategies are being used by patients, particularly in terms of the frequency of use and sequencing of treatments. The group also acknowledged the need to study how treatment choices vary based on patient characteristics such as childbearing aim, age, insurance status, and other social/cultural factors, and concluded that prospective studies may be necessary to answer these questions due to the limitations of existing data. (See the discussion in the Clinical Background section).

Methods

The TWG discussed the need for methods development to support uterine fibroid research. The group identified three areas for methods development: anatomical classification systems, patient-reported outcomes, and measures of treatment response. First, the group discussed the need for a widely accepted and thorough anatomical classification system for uterine fibroids. While the European Society of Hysteroscopy (ESH) system classifies fibroids based on anatomical location, the system lacks any categorization based on the size of the fibroid and does not account for multiple fibroids.[44] Participants noted that a new classification system, the "Bethesda" system, is currently in development but needs additional funding to be finalized and validated.[45] This system defines multiple fibroids by location and includes information on the size of the fibroids. The lack of a standard scoring system creates ambiguity in the classification and description of uterine fibroids among practicing clinicians and limits the ability of researchers to aggregate data from multiple studies in meta-analyses. As a result, it is difficult for clinicians and researchers to understand the relationships between fibroid size and location and disease presentation and symptoms.

Second, the TWG reviewed the need for new patient-reported outcome (PRO) measures to assess symptom reduction in patients undergoing treatment for uterine fibroids. The only PRO instrument specific to uterine fibroids is the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL).[46] The UFS-QOL has been validated previously. However, the validation did not include a longitudinal assessment (before and after treatment), and the women participating in the validation were younger than typical uterine fibroid patients. The TWG also noted that the U.S. Food and Drug Administration (FDA) recommends using PROs as primary outcomes only when they have been validated sufficiently, highlighting the need to create fully validated tools.

Lastly, the TWG emphasized the need to develop new tools to assess and report symptoms. Currently, clinicians can use menstrual pictograms, menstrual diaries, and the alkalin hematin method (see glossary in Appendix F) to assess the presence of symptoms, but these methods are burdensome to patients and difficult to use, a situation that limits their utility in research studies. Further, the current methods do not measure the sum of fibroid symptoms, including nonbleeding symptoms such as pain, pressure, and urinary symptoms. The participants concluded that the lack of a widely accepted anatomical classification system, combined with the lack of fully validated PRO and symptom measures, may inhibit the ability of researchers to answer questions about the relative effectiveness of treatments.

Natural History

The TWG suggested that studies of the natural history of uterine fibroids are needed to help inform comparative effectiveness research. The natural history of uterine fibroids, in terms of fibroid growth, shrinkage, and symptomatology, is not well understood. The recent Fibroid Growth Study provided some insights into the growth and regression of uterine fibroids, but the study was limited in terms of sample size and duration.[47] Future research should also address factors that influence the natural history of uterine fibroids, such as age, race/ethnicity, reproductive history, family history, and menopausal status. In addition, research in this area should gather new information on the incidence and prevalence of uterine fibroids in the United States. The existing literature in this area focuses on specific geographic areas, such as the eastern seaboard of the United States, or on specific subpopulations, such as African American women.[48,49] However, any large longitudinal study of the incidence, prevalence, or burden of disease would need to include standardized confirmation of fibroids and address common difficulties such as loss to followup. Additionally, studies to determine the overall incidence and prevalence of nonsymptomatic uterine fibroids would be challenging because fibroids are not usually detected until they cause symptoms.

Care Coordination/Shared Decisionmaking

The TWG members added new research questions on care coordination/shared decisionmaking. A 2007 AHRQ Technical Review defines care coordination as "the deliberate organization of patient care activities between two or more participants (including the patient) involved in a patient's care to facilitate the appropriate delivery of health care services."[50] AHRQ defines shared decisionmaking as "a model of patient-centered care that enables and encourages people to play a role in the management of their own health" and that "operates under the premise that, armed with good information, consumers can and will participate in the medical decisionmaking process by asking informed questions and expressing personal values and opinions about their conditions and treatment options."[51]

The TWG members, particularly those representing the patient and consumer perspective, emphasized the need to understand how patients and providers acquire information and make treatment decisions for uterine fibroids. Specifically, the TWG underscored the need to study how current strategies for care coordination among providers and for shared decisionmaking between patients and providers influence outcomes. The TWG noted that the answers to these research questions would facilitate the translation and dissemination of future research findings. The members also cautioned that data on treatment patterns and the factors influencing patient choice are necessary to an understanding of current methods of care coordination and shared decisionmaking. In addition, the called for further research on the comparative effectiveness of the available management options to inform the development of strategies for care coordination and shared decisionmaking.

Genetics

The TWG discussed the need for new research examining how genetics and genetic factors may influence the development, growth, and treatment of uterine fibroids. Members suggested that determining how genetic factors differ by race or ethnicity may help identify subgroups that are at highest risk and allow for the targeting of therapies for specific subpopulations. Increased knowledge in this area may inform studies of the natural history of uterine fibroids as well. The TWG suggested that research in this area should include gene and environmental interactions, such as lifestyle and diet. Members also noted that the current investments in personalized medicine provide an opportunity for increased research in this area.

The Technical Working Group's Refined List of Research Questions

Based on the discussion at the in-person meeting, the TWG revised the list of research questions. The revised list of research questions, organized by category, is provided below.

Patterns of Use

- What individual strategies (e.g., watchful waiting, lifestyle changes) or combinations (including different sequencing) of strategies are most frequently used as treatment in fibroid management? How does this vary by patient characteristics (childbearing aim, age, language, demographics, insurance status, provider characteristics, patient preference, social/cultural factors, and geography)?

Methods

- What are the characteristics of validated and reliable classification systems of standard anatomic staging to use in research and clinical care of women with uterine fibroids?
- What are the characteristics of validated and reliable classification systems of patient-reported outcomes (including patient preferences, disease-specific and general quality of life, and patient satisfaction) to use in research and clinical care of women with uterine fibroids?
- What are the characteristics of validated and reliable classification systems of measures of responses to specific symptoms (such as menstrual pictograms, menstrual diaries, hemoglobin) to use in research and clinical care of women with uterine fibroids?

Natural History

- What are the incidence, prevalence, and burden of disease (accounting for misclassification of symptoms) of fibroids in the United States?

- What is the natural history of uterine fibroids in terms of fibroid growth, regression, and symptomatology among women who choose watchful waiting over durations longer than 6 months? What factors (including age, race/ethnicity, smoking status, reproductive history, history of contraceptive use, body mass, family history, and menopausal status) affect the natural history of disease?

Genetics

- Are there genotypes, gene mutations, gene/environment interactions, epigenetic modifications, or other biomarkers that differ by race or ethnic group that may account for differences in the incidence, natural history, and treatment response (including rate of growth and symptom patterns) of disease among these groups?

Care Coordination and Shared Decisionmaking

- How do patients and providers currently identify and choose strategies for fibroid management (including acquisition and processing of available information and patient-provider communication)?
- How do different strategies for shared decisionmaking affect outcomes, especially patient reported outcomes?
- What are the most effective dissemination approaches for providing patients and providers with the best evidence on fibroid management, and do these vary across different subpopulations?
- What methods of coordinating care among different providers are most effective in improving outcomes?

Relative Effectiveness

- What is the relative effectiveness of the available procedural or nonprocedural treatments for uterine fibroids?
- What are the most important subpopulations to predefine (e.g., childbearing aim, race/ethnicity, age, and therapeutic goals)?
- What are the most important outcomes to measure (e.g., anatomical, durability of symptom relief, patient-reported outcomes, cost, impact on reproductive outcomes, and patient satisfaction)?
- What are the most important treatment options to study?
    - Procedural treatments (e.g., hysterectomy, myomectomy, uterine artery embolization (UAE), magnetic resonance image-guided focused ultrasound, endometrial ablation)
    - Nonprocedural treatments (e.g., hormonal therapies, oral contraceptives, and nonsteroidal anti-inflammatory drugs)
    - Complementary and alternative medicine
    - Lifestyle changes
    - Watchful waiting (no treatment)

After the meeting, the TWG members rated the refined set of research questions using the online scoring tool. The goal of this round of scoring was to provide a baseline rating of the research questions to aid the discussions at the Stakeholder Committee meeting. In addition to rating the questions, TWG members estimated the necessary duration of a study to address each question and indicated whether a single study could address more than one question

simultaneously. TWG members also prioritized the subpopulations, outcomes, and interventions included in the relative effectiveness subquestions.

The TWG rated as the highest priorities research questions related to the relative effectiveness of uterine fibroid interventions and methods for creating classification systems. For the relative effectiveness subquestions, the TWG rated procedural and nonprocedural treatments as the most important treatment options to study. Durability of symptom relief was rated the most important outcome to measure, followed by the impact on reproduction and patient-reported outcomes. Childbearing aim was rated the most important subpopulation to predefine, followed by age and race/ethnicity. The TWG estimated that research studies to address the relative effectiveness questions would take more than 5 years to complete. The group suggested that other studies, including those related to classification systems, care coordination, and shared decisionmaking, could be completed in shorter timeframes.

In their comments, some TWG members emphasized that the methods-related questions may need to be addressed first, to enable proper study of the relative effectiveness question. Members also suggested that, without further prioritization of the subquestions, multiple studies would be needed to answer the relative effectiveness question. In addition, members noted that the patterns of use, natural history, and care coordination questions may be assessed in a single survey that includes sections for providers and patients. The results from the second round of scoring are provided in Appendix E.

Stakeholder Committee: Review and Prioritization of Research Questions

Materials To Inform the Priority-Setting Process

The project team developed background materials for the Stakeholder Committee to inform and facilitate the priority-setting process. These materials included a background document on uterine fibroid disease, an overview of the project objectives and the priority-setting process, a description of the priority-setting criteria, and background briefs for each research topic area. The background document provided a succinct overview of uterine fibroid disease, including the symptoms, treatments, natural history, incidence, and prevalence of the disease. In addition, the document briefly summarized the limitations of current evidence and explained why evidence gaps exist. The background briefs provided more in-depth information on each of the research question topic areas. Each brief described the existing research in the topic area, limitations of that research, and issues that may complicate future research in the area. The project team developed these briefs in consultation with the TWG. The purpose of these documents was to ensure that all Stakeholder Committee members had a common understanding of the current state of evidence in uterine fibroid disease and the issues related to conducting research in this disease area.

After distributing the materials, the project team hosted a teleconference with patient and consumer representatives. Based on previous experience, the project team determined that convening the patient and consumer representatives prior to the in-person meeting would help to facilitate their active participation. The objectives of the teleconference were to review the priority-setting process and the background materials, discuss specific patient/consumer concerns, and obtain feedback about the suitability of the background materials. The call also emphasized the importance to the success of the project of the patient and consumer representatives' participation. During this call, representatives raised several concerns and offered suggestions, and the project team attempted to address these concerns before the in-person meeting. Representatives also suggested including a session at the meeting where patients

and consumers could describe the difficulties they faced when seeking treatment for uterine fibroids. The goal of this session was to remind other stakeholders that the prioritized research agenda should emphasize questions that would improve the quality of care for patients. Following the patient and consumer representative pre-meeting call, the project team felt that the call was very important in explaining the purpose of the in-person meeting and addressing potential concerns in advance of that meeting.

Stakeholder Committee Discussions

The primary objectives of the Stakeholder Committee in-person meeting were to discuss and prioritize the 12 research questions recommended by the TWG. To avoid biasing the Stakeholder Committee, the questions were discussed by research topic rather than in the priority order identified by the TWG. Members of the TWG and project team led the sessions on each research topic by first presenting background information on the topics and then moderating the discussion. Highlights of the discussion around each category are provided below.

Relative Effectiveness

The relative effectiveness discussion focused on the need to define the treatment options, subpopulations, and outcomes of interest. Stakeholder Committee members asked for clarification about the purpose of predefining subpopulations for a study. The project team explained that the study population and the treatment options and outcomes of interest for a study are closely linked. For example, a study that enrolls women who wish to bear children in the future may consider different treatment options and use different measures of effectiveness than a study of women who do not wish to bear children in the future. The goal of the discussion was to determine whether it is necessary to narrowly focus a study on a specific subpopulation, and, if so, which subpopulation or populations.

Stakeholder Committee members asked for similar clarifications for the term "therapeutic aim." The project team explained that therapeutic aims influence the design of a study. For example, one therapeutic aim may be to control bleeding, while another may be to relieve pressure. An effectiveness study may use a different design, depending on the therapeutic aim of interest. The group noted that the most important outcomes to study would vary depending on the severity of the disease in the patients under study. Conversely, the most important treatment options to study would be driven by the patient's treatment goals. For example, patients whose primary concerns are reproductive outcomes will not consider studies that include hysterectomy as a treatment arm.

Note, that, for the purposes of this paper, the term "procedural" refers to procedure-based treatment strategies (including surgical and nonsurgical) while the term "nonprocedural" refers to medical therapies used primarily for treatment of symptoms. In order to address the diversity of views, the project team raised a new question on the importance of procedural treatments versus nonprocedural treatments. At this point in the day, participants suggested that the most important questions related to studying the relative effectiveness of treatment pathways that begin with procedural versus nonprocedural treatments, followed by studying the relative effectiveness of the different procedural treatments. A small number of participants prioritized studying watchful waiting and complementary and alternative medicine. In subsequent discussions, participants noted that using watchful waiting as a control arm raises ethical issues. Once symptoms appear, most women try some form of treatment, such as oral contraceptives or pain medication. The group felt that it might not be ethical to ask women to do nothing to treat their symptoms.

In terms of subpopulations, stakeholders identified childbearing aim and therapeutic goals as the most important groups to predefine. Stakeholders also suggested that patient-reported outcomes (PROs), durability of symptom relief, and reproductive outcomes were the most important outcomes to measure. Stakeholders were also asked to identify the most important procedures to include in a study. Participants noted there were still many outstanding questions about the effectiveness of UAE and focused ultrasound, despite the fact that these are widely used. Patient representatives emphasized the importance of gathering new information on the less invasive alternatives to hysterectomy. A payer representative commented that focusing on these types of procedures would support patient-centric research in an area where there are critical gaps in the evidence.

In discussing procedural treatments, several participants raised specific concerns about hysterectomy, which is the most commonly used surgical procedure for uterine fibroids. Participants suggested that the long-term consequences of the procedure are unknown. One participant noted the challenges related to studies of long-term risk. For example, is impact on mortality the most appropriate outcome? If not, what would be the most meaningful outcomes for judging long-term risks? In addition, several different methods for performing hysterectomies are now available, but little information exists on the relative risks and benefits of these methods. Despite the fact that hysterectomy is considered the definitive treatment for uterine fibroid disease, patient representatives also suggested hysterectomy is a last resort for most women. One participant mentioned that it is very difficult to randomize participants to hysterectomy treatment arms in trials and that the best method for doing so might be to recruit women who had already agreed to a hysterectomy.

There was additional discussion on the importance of comparing nonprocedural treatments to procedures as broad categories. Analyses of claims data have shown that medical treatment is the most common treatment. Many women use hormonal therapy or pain medications when symptoms first appear, and the majority of women do not escalate quickly to procedures. Over time, however, claims data show an escalating pattern of treatments that become more intensive, ultimately resulting in procedures. Several participants agreed that designing a study to reflect the pathways of care and including comparison groups that describe the actual treatment options women face would be valuable. For example, a study could be designed to recruit patients early in the disease trajectory where a woman first faces a decision to use a procedure or to continue with pharmacotherapy. The care pathway for initially selecting medical therapy would include subsequent procedures.

A similar study has been done in bipolar disease. The Systematic Treatment Enhancement Program for Bipolar Disease (STEP BD Trial) explored a range of treatment options and defined a best practice care pathway.[52] The study used decision trees comparing defined pathways. One participant noted that focusing a comparative effectiveness study in uterine fibroids on comparing treatment A versus treatment B would not answer the questions facing women over the course of their disease. Designing a study of treatment pathways will be very complex, since information on treatment patterns, particularly on use of lifestyle interventions or alternative therapies, is currently lacking. One participant noted that many step therapy programs compare progression of interventions that have known effectiveness in at least some subpopulation, which is not true for many of the alternatives used to treat uterine fibroids. Based on the discussion, it became clear that the key decision for the group was whether it was more important to directly compare different procedures or to study different treatment

pathways. A majority of the group recommended that it was most important to study treatment pathways following an initial treatment decision.

Methods

This discussion addressed the three methods research questions:

- What are the characteristics of validated and reliable classification systems of standard anatomic staging to use in research and clinical care of women with uterine fibroids?
- What are the characteristics of validated and reliable classification systems of patient-reported outcomes (including patient preferences, disease-specific and general quality of life, and patient satisfaction) to use in research and clinical care of women with uterine fibroids?
- What are the characteristics of validated and reliable classification systems of measures of response to specific symptoms (such as menstrual pictograms, menstrual diaries, hemoglobin) to use in research and clinical care of women with uterine fibroids?

The system currently used for classifying fibroids was developed in 1918 and has not been updated. This system classifies fibroids by their location in the uterus but it does not capture the size or severity of the fibroids. One of the challenges in creating a new anatomical classification system is that both the size and location of uterine fibroids are continuous variables. Thus, attempts to describe these variables with discrete definitions leads to imprecision. In addition, uterine fibroids do not automatically progress. Some may even decrease in size and current classification systems do not account for this. One participant recommended that anatomical staging systems should also have some predictive value and should not just describe the uterine fibroids. However, other participants noted that just having a reliable method of classifying fibroids by size and location would be helpful. Currently, researchers are unable to reliably characterize the patients enrolled in their studies, which limits the potential for systematic reviews to aggregate the data for meta-analysis. Participants also noted that there is no way to know if certain variables used for anatomical classification are predictive until those variables are defined. Developing large predictive models is also not possible without a reliable staging system.

Several of the Stakeholder Committee members have been involved in a separate project to create a reliable anatomical classification system. That project used a modified Delphi technique with a group of 12 stakeholders to develop a draft classification system, which they named the Bethesda Classification system. The draft classification system is now complete, but it must be tested and validated.

Regarding the second question on developing reliable measures for PROs, participants noted that the UFS-QOL is a validated instrument specifically designed for uterine fibroid disease. Although this measurement tool is extremely useful, its utility is limited in several ways. First, the lack of a corresponding standard classification system for rating the size and severity of fibroids makes it difficult to interpret results based on UFS-QOL. Second, this PRO measure currently does not capture other important patient information such as childbearing aim and how patients make choices about treatment. One participant also mentioned that it would be important for the selected PRO measure(s) to be acceptable to the FDA, should the data be used for reporting to the FDA for some purpose. The FDA evaluates PRO measures against its published PRO guidance.[53] Another issue related to PRO measures is the appropriate time interval between the intervention and followup. This issue is particularly salient for uterine fibroids because

symptom severity can vary significantly from month to month, and it may be useful to collect PROs more often.

The third question in this section focused on measures of response for specific symptoms. Current measures include menstrual pictograms, menstrual diaries, and alkaline hematin. Participants noted that these measures are extremely important in studies of new treatments that are being submitted to the FDA for marketing approval. However, participants noted that using some of these measures, such as alkaline hematin, is burdensome and inconvenient for the patient and expensive for the study. It was also mentioned, based on the experience of one of the participants, that the most commonly used measure is the menstrual pictogram, which has been validated in a number of large studies. However, this measure has to be revalidated frequently due to changes in products and treatments over time.

Natural History and Patterns of Care

This discussion addressed the three questions on incidence and prevalence of the disease, its natural history, and patterns of care:

- What is the incidence, prevalence, and burden of disease (accounting for misclassification of symptoms) of fibroids in the United States?
- What is the natural history of uterine fibroids in terms of fibroid growth, regression, and symptomatology among women who choose watchful waiting over durations longer than 6 months? What factors (including age, race/ethnicity, smoking status, reproductive history, history of contraceptive use, body mass, family history, and menopausal status) affect the natural history of disease?
- What individual strategies (e.g., watchful waiting, lifestyle changes) or combinations (including different sequencing) of strategies are most frequently used as treatment in fibroid management? How does this vary by patient characteristics (childbearing aim, age, language, demographics, insurance status, provider characteristics, patient preference, social/cultural factors, and geography)?

In discussing the question on incidence, prevalence, and burden of disease, participants mentioned that existing research is limited to a few studies that derived primarily from centers on the east coast of the United States and in a few European countries. Although these were strong studies, they only answer this question for select populations. Obtaining data to examine this question in broader populations is difficult because there are no national databases with this information. Participants also debated whether estimates of incidence and prevalence should include asymptomatic patients, although they noted that gathering data on these patients would be difficult. Additionally, stakeholders mentioned that adequately addressing questions related to the incidence, prevalence, natural history, and burden of disease for uterine fibroids would require a significant investment and a long-term study. Patient and consumer representatives emphasized the importance of including the people who are not typically studied, such as teenage women and those from minority groups (e.g., Hispanic, tribal, and Asian heritage), in any such study. Some participants suggested that a national screening campaign might be one possible model for engaging people in a study of this type.

In discussing the natural history question, one participant raised ethical concerns related to studying the natural progression of uterine fibroids without offering any form of intervention to patients. Several participants mentioned that the only individuals who would tolerate watchful waiting are those individuals with asymptomatic fibroids, but locating individuals with asymptomatic fibroids is difficult as these patients may not seek care or may not even know that

they have fibroids. However, capturing information on the natural history of disease is necessary to facilitate the development of new treatments.

In discussing the patterns of care question, participants emphasized that answering this question is critical to an understanding of the treatment pathways that patients follow. Both physicians and payers play a major role in defining treatment pathways for women suffering from this disease. While one participant suggested private payer datasets might be informative to understand patterns of care, others noted the limitations of these data. Individuals often do not stay with the same insurance companies for long periods, so there is loss to followup with many patients. In some cases, individuals pay for uncovered services themselves and these data are not available in the datasets. Other factors, such as income, information on presenting symptoms, and other comorbidities, are also not captured. All of these factors potentially confound the analyses of the data. One participant suggested that data from integrated health plans (such as Kaiser) that can link medical records to claims data might be best for addressing these questions.

Participants also recommended that studies designed for this question account for treatment variations by demographic characteristics. For example, treatment options in rural areas, where patients may not have access to specialists, may differ from treatment options in urban centers where patients have access to new technologies. Understanding the geographic variability in the use of various management options is important to developing new CER and disseminating the results.

Care Coordination and Shared Decisionmaking

This discussion addressed the four questions related to care coordination and shared decisionmaking:

- How do patients and providers currently identify and choose strategies for fibroid management (including acquisition and processing of available information and patient-provider communication)?
- How do different strategies for shared decisionmaking affect outcomes, especially patient reported outcomes?
- What are the most effective dissemination approaches for providing patients and providers with the best evidence on fibroid management, and do these vary across different subpopulations?
- What methods of coordinating care among different providers are most effective in improving outcomes?

Members of the Stakeholder Committee indicated that, for shared decisionmaking to work, physicians must be engaged since patients generally trust the advice that physicians provide (a claim that was strongly endorsed by one of the patient representatives). The patient representatives also noted that many women report that hysterectomy was the only treatment option presented to them. Therefore, developing better ways to educate both physicians and patients about treatment options is necessary. This can be accomplished through multiple channels such as print, Internet, DVDs, or other media that disseminate the necessary information. In addition, further research is needed to understand which types of materials work best for whom.

Shared decisionmaking can also be an important tool to reduce bias in treatment selection and improve patient empowerment. Improving shared decisionmaking in this area will likely affect how individuals make health care decisions in all areas and could therefore, as one participant noted, "benefit women in a much broader way over a lifespan." Participants

suggested that patients need to be aware of how little is known about the various treatment options and what their potential risks and benefits are. One payer representative indicated that shared decisionmaking models for breast cancer and benign prostatic hyperplasia implemented by his organization have successfully improved patient-provider communication as well as the dissemination of information.

In terms of care coordination, one meeting participant mentioned that care coordination is now becoming a professional expectation.

Genetics

This discussion focused on the genetics question: are there genotypes, gene mutations, gene/environment interactions, epigenetic modifications, or other biomarkers that differ by race or ethnic group that may account for differences in the incidence of disease, natural history, and treatment response (including rate of growth and symptom patterns) among these groups?

This question differs from other questions related to epidemiology and natural history of disease because it focuses primarily on the biological mechanisms underlying the disease, and pathophysiological pathways may affect outcomes for women with uterine fibroids. Participants indicated that this question was of great importance because the use of genomics to decide who needs to be screened, to predict patient-specific responses to treatment, and to predict disease recurrence would represent tremendous progress in the field. However, these goals will require many years of research, and currently little data exist on genetics and uterine fibroids. As a first step, research can focus on understanding the basic genetic mechanisms of the disease, so that physicians can predict disease severity and have a better understanding of when intervention is appropriate. Learning more about molecular genomics would also support the development of alternative therapies for women who are at risk of developing symptomatic fibroids, with the goal of preventing fibroid development.

Patient representatives noted that they often wonder why they developed fibroids and whether the disease was inherited. One patient mentioned that her grandmother and mother had fibroids, and she is concerned that her daughter will as well. Participants suggested that a family registry might be valuable for understanding gene/environment interactions as families often live in similar environments and have similar diets.

Participants also noted that uterine fibroid disease is currently viewed as a single condition. Because age at presentation and number and size of fibroids vary among women, it is likely that many different conditions are currently labeled as uterine fibroid disease. Evidence on genetic mechanisms will be helpful in differentiating these conditions. Participants also noted that there were several subquestions embedded in the general genetics question. To begin addressing these questions, researchers could examine fibroid tissue samples for gene mutations that affect size, number, or locations of the fibroids; researchers could also look for biomarkers in serum samples, as these samples are much easier to collect. Tissue samples can only be collected from women who have undergone an invasive procedure, which excludes an important subset of women with fibroids and requires more resources to collect, store, and study. Additionally, tissue samples must be studied fairly soon after they are collected. Due to these limitations, participants suggested that studying bioserum samples should be a higher priority.

Patient and Consumer Forum

During the meeting, the patient and consumer representatives on the Stakeholder Committee were given the opportunity to describe either their direct experience dealing with uterine fibroids or their experience in helping those women who were suffering from the disease.

These representatives raised several critical points. First, they noted that to increase participation in research studies, patients must understand the importance of the research and the extent of current evidence gaps. Second, patients want to know why they developed the disease. Several patients indicated that they wondered whether fibroids were caused by genetics and inherited through family or whether the development of fibroids was caused by their actions, such as using oral contraceptives for extended periods. Patient and consumer representatives also stressed the importance of disseminating the results from research in ways that patients, who need the information to make informed treatment decisions, can easily comprehend. They also emphasized that cultural and family influences significantly affect patients' decisions regarding watchful waiting and treatment. Patients indicated that the field has advanced significantly since their mothers and grandmothers were treated for fibroids, but they also think research has a long way to go. Finally, patients and consumers expressed their appreciation for being included in the project and stressed that it is critically important that researchers and others involved in the process remember the "human factor."

Prioritization of the Research Questions by the Stakeholder Committee

After this rich discussion about the relative merits of the proposed research agenda, stakeholders provided feedback on the final set of research questions, using the priority-setting criteria provided in Table 1. In response to the discussion in the morning, the question on relative effectiveness was reshaped into the following two research questions:

- What is the relative effectiveness of available procedural versus nonprocedural (medical) treatments as initial therapy, on durability of symptom relief and patient-reported outcomes?
- What is the relative effectiveness of available procedural treatments (e.g., hysterectomy, myomectomy, uterine artery embolization (UAE), magnetic resonance image-guided focused ultrasound, endometrial ablation) on durability of symptom relief and patient-reported outcomes?

The prioritization was done as a group, using an audience response system as an interactive aid in the group discussion. Each question was dynamically prioritized on the screen as different stakeholders provided feedback through an individual keypad. Each keypad was identifiable by self-described stakeholder subgroup (patients, clinicians, Federal, insurer, industry) gathered at the start of the discussion. The audience response system enabled review of the prioritizations in aggregate and by these subgroups, while leaving the individual stakeholders anonymous (see Table 2).

The final highest priority questions for the overall group were the two relative effectiveness questions, with slight preference given to comparisons among different procedural treatments. This result differed only slightly from the morning result (which identified procedural treatments versus nonprocedural treatments as the highest priority) and confirmed that both questions were considered high priority by the majority of the stakeholders at the meeting. Table 2 provides the top two questions by stakeholder group for additional perspective. Every subgroup of the Stakeholder Committee maintained at least one of these two questions in its top two.

Table 2. Top two highest priority questions by stakeholder group

	Patients	Clinicians	Federal	Insurer	Industry	Overall
1.	Relative effectiveness of procedural treatments	Relative effectiveness of procedural vs. nonprocedural treatments	Relative effectiveness of procedural vs. nonprocedural treatments	Relative effectiveness of procedural treatments	Relative effectiveness of procedural treatments	Relative effectiveness of procedural treatments
2.	Validated and reliable measures of patient-reported outcomes	Relative effectiveness of procedural treatments	Relative effectiveness of procedural treatments	Dissemination of results to patients and providers	Validated and reliable measures of patient-reported outcomes	Relative effectiveness of procedural vs. nonprocedural treatments

As shown, different stakeholder groups had varying degrees of consensus with the overall priorities of the group, demonstrating the importance of having a diverse group of stakeholders. For instance, clinicians and Federal representatives identified determining the relative effectiveness of procedural versus nonprocedural treatments as a higher priority than determining the relative effectiveness of procedural treatments alone. For payers, relative effectiveness of available procedural treatments was top, but dissemination of results to patients and providers was also very important. Payers also noted that it was very important to improve methods for shared decisionmaking. This focus underscores perspectives raised in earlier discussions, where payer representatives felt that physicians were driving treatment choices and that shared decisionmaking models had the potential to refocus treatment selection to reflect patient concerns. Finally, in addition to relative effectiveness, patient representatives also thought that the development of validated and reliable measures of patient-reported outcomes and studies on the genetic components of uterine fibroids should be high research priorities. It should be noted that the results of the overall prioritization were reviewed with and without the input of the industry group, and the top priority questions and their relative order remained unchanged.

The prioritization of the questions by the TWG and the Stakeholder Committee also produced largely similar results. Table 3 below compares the prioritizations of each group. Both groups ranked the relative effectiveness question as the highest priority. Both groups also identified methods-related questions as high priority areas.

Table 3. Comparison of TWG and stakeholder committee prioritizations

Question	TWG Prioritization	Stakeholder Committee Prioritization
What is the relative effectiveness of the available procedural or nonprocedural treatments for uterine fibroids?	1	N/A (this question was split into the 2 questions below at the Stakeholder Committee meeting)
What is the relative effectiveness of available procedural treatments (e.g., hysterectomy, myomectomy, uterine artery embolization (UAE), magnetic resonance image-guided focused ultrasound, endometrial ablation) on durability of symptom relief and patient reported outcomes?	N/A (this question was developed at the Stakeholder Committee meeting)	1
What is the relative effectiveness of available procedural vs. nonprocedural (pharmacotherapy) treatments as initial therapy on durability of symptom relief and patient-reported outcomes?	N/A (this question was developed at the Stakeholder Committee meeting)	2

Table 3. Comparison of TWG and stakeholder committee prioritizations (continued)

Question	TWG Prioritization	Stakeholder Committee Prioritization
What are the characteristics of validated and reliable classification systems of patient reported outcomes (including patient preferences, disease-specific and general quality of life, and patient satisfaction) to use in research and clinical care of women with uterine fibroids?	2	4
What are the characteristics of validated and reliable classification systems of standard anatomic staging to use in research and clinical care of women with uterine fibroids?	3	3
What are the incidence, prevalence, and burden of disease (accounting for misclassification of symptoms) of fibroids in the United States?	4	10
What is the natural history of uterine fibroids in terms of fibroid growth, regression, and symptomatology among women who choose watchful waiting over durations longer than 6 months? What factors (including age, race/ethnicity, smoking status, reproductive history, history of contraceptive use, body mass, family history, and menopausal status) affect the natural history of the disease?	5	7
What are the most effective dissemination approaches for providing patients and providers with the best evidence on fibroid management, and do these vary across different subpopulations?	6	8
How do patients and providers currently identify and choose strategies for fibroid management (including acquisition and processing of available information and patient-provider communication)?	7	11
Are there genotypes, gene mutations, gene/environment interactions, epigenetic modifications, or other biomarkers that differ by race or ethnic group, that may account for differences in the incidence of disease, natural history, and treatment response (including rate of growth and symptom patterns) among these groups?	8	6
What individual strategies (e.g., watchful waiting, lifestyle changes), or combinations (including different sequencing) of strategies are most frequently used as treatment in fibroid management? How do these strategies vary by patient characteristics (childbearing aim, age, language, demographics, insurance status, provider characteristics, patient preference, social/cultural factors, and geography)?	9	9
How do different strategies for shared decisionmaking affect outcomes, especially patient-reported outcomes?	10	12
What are the characteristics of validated and reliable classification systems of measures of responses to specific symptoms (such as menstrual pictograms, menstrual diaries, hemoglobin) to use in research and clinical care of women with uterine fibroids?	11	5
What methods of coordinating care among different providers are most effective in improving outcomes?	12	13

Lessons Learned and Limitations

To develop a prioritized research agenda, the project team used a modified Delphi method technique involving both the small TWG and the larger Stakeholder Committee. This process had a number of strengths, which are discussed in more detail below.

Utilizing a Small TWG To Help Narrow the Initial List of Research Questions

The project team relied heavily on the TWG members both for narrowing the initial list of research questions and for refining the wording of research questions during the process. Performing these tasks with a larger group would not have been possible. In addition, the project team relied on the members of the TWG to lead the discussions during the in-person meeting of the Stakeholder Committee because this group has a broad range of clinical and practical expertise in this area. These individuals formed a core of thinkers who carried their consensus, confidence, and expertise into the larger stakeholder meeting. Using the TWG members to summarize particular topic areas and lead the discussion provided credibility and energy that helped advance the discussion.

Including a Wide and Balanced Array of Perspectives in Both the TWG and Stakeholder Committee

Stakeholders represented in this process included patients and consumers, physicians, researchers, payers, representatives from government agencies, and manufacturers. During the meetings, each stakeholder group raised different issues and considered the problem through a slightly different lens, which was invaluable to the process. Ensuring that there was balance in the group increased individuals' level of comfort in engaging in group discussions and raising potentially controversial points. The balance also prevented a single stakeholder group from dominating the conversation. Patient and consumer representatives were appreciative of being included in the TWG, and their involvement resulted in new patient-focused questions being added to the prioritized list. None of these new questions had been identified as priorities by researchers completing prior systematic reviews. The inclusion of patient representatives and the diversity of perspectives in both the TWG and Stakeholder Committee are consistent with the goals of the EHC Program, which emphasize developing evidence and products that meet the needs of patients, consumers, clinicians, and policymakers.

Allowing for In-Person Meetings of Both the TWG and Stakeholder Committee

Getting these individuals together face-to-face allowed people to interact with each other, get to know one another, and stay focused on the task presented to them. Meeting in person was essential to being able to reach consensus on the most important issues. Many stakeholders involved in this project expressed their appreciation at being able to meeting with other stakeholders in person.

Using Proactive Approaches To Engage Patients and Consumers

An important aspect of this project was engaging patients and consumers. Based on previous experience, the project team felt that including several patient and consumer representatives would make these individuals feel comfortable expressing their opinions in meetings. The project team recruited two patient and consumer representatives for the TWG and four for the Stakeholder Committee. In addition, background materials were prepared so that they could be easily understood by patients and consumers, and a pre-stakeholder-meeting call was held with all patients and consumers to address any outstanding questions or concerns.

During this call, patients and consumers expressed their desire to have a time during the stakeholder meeting to discuss their experience with uterine fibroids, so that other stakeholders could be more aware of the struggles they faced and so that researchers would remember the goal of the research—to improve outcomes for patients. The project team added a patient and consumer panel, which was an invaluable component of the Stakeholder Committee meeting. The active involvement of patient and consumer representatives was critical to ensuring that the final stakeholder-driven research agenda is reflective of the views of all major stakeholder groups. This aspect of the project also supported AHRQ's goals of supporting patient-driven research.

There are also a number of areas for improvement, several of which are discussed below.

Managing the Initial List of Research Questions

The TWG expressed concern about repetitiveness in the initial list of research questions, and suggested that the project team should have refined the list before asking the TWG to provide their initial scores. Having multiple repetitive questions increases the time it takes to complete the scoring process and does not add value to the process. More time at the beginning stages of the process is needed to ensure that questions are clear and that each evidence gap is covered by a single research question.

Limited Value of Scoring the Refined Research by Each of the Priority-Setting Criteria

After the TWG in-person meeting, TWG members were asked to score each of the research questions based on each of the priority-setting criteria on a scale of 0–10. Because not all of the criteria apply to each of the questions, this exercise was unnecessary. Asking the TWG members to consider each criterion as they decide on a final, overall score would have been sufficient.

Need To Reduce the Amount of Materials Provided to the TWG and Stakeholder Committee

Members of the TWG and members of the Stakeholder Committee agreed that the amount of material given to them prior to the meetings, although helpful, exceeded what could be reasonably reviewed. Having more time to develop these materials might have made it possible to condense and reduce the number of items that were sent to the participants. Still, ensuring that participants are adequately prepared to engage in meaningful discussions, without potentially overburdening them, is a difficult balance to achieve, particularly given the various backgrounds of the Committee members. Sending a hardcopy set of the materials, rather than an emailed document, may have been useful, but would have required additional time and budget.

Clarity and Context of Research Questions

For several of the research questions, participants asked for clarity regarding the meaning of the question. In future projects, providing a brief explanation for each question would be useful. In addition, limiting the number of subquestions contained within a specific research question is important to improve the clarity of the questions. For example, the question related to genetics included several subquestions, making it difficult to have an in-depth discussion of the question. Research questions should be formulated in such a way that they only address one issue and should be stated as clearly and concisely as possible.

In addition to these lessons learned, it is important to note the potential limitations of the priority-setting and stakeholder engagement processes used in this project. First, the members of

the Stakeholder Committee were not evenly divided among the five stakeholder groups. It is possible that the uneven numbers of Committee members in the various groups allowed some groups to have greater weight in the priority-setting process. However, analysis of the prioritization results at the stakeholder group level showed that each group considered the relative effectiveness question as one of the top two highest priority questions. Therefore, it is unlikely that the numerical apportionment of the representatives to the Stakeholder Committee affected the identification of the highest priority research question, although it may have affected the priority order of the remainder of the questions.

A second limitation relates to the sequencing of research. The potential research questions included foundational research questions, such as those related to understanding the natural history of the disease and developing new methodologies. It is possible that these questions need to be addressed prior to developing studies on relative effectiveness or care coordination. The process of having stakeholders rank each question as if they have equal value and feasibility in the research sequence may allow stakeholders to overlook the need for foundational research in favor of other questions that are perceived as more interesting. However, the TWG and Stakeholder Committee each discussed research sequencing in the in-person meetings, and participants were asked to consider the feasibility of designing a study to address the research question during prioritization activities. The fact that the relative effectiveness questions were ranked as higher priorities by both groups suggests that the participants feel that addressing the methods-related questions is not a prerequisite to studying relative effectiveness

It should also be noted that the project is still underway. Additional limitations or lessons learned may be discovered during the next phases of the project or at the close of the project, when feedback is solicited from the Stakeholder Committee and TWG.

Research Agenda for Uterine Fibroid Disease

Prioritized Research Questions

The result of the priority-setting process described above is a prioritized list of the most important research questions related to the management of uterine fibroid disease. The prioritization activity conducted during the afternoon session of the in-person Stakeholder Committee meeting was used to assemble the final, prioritized list. The list of questions, in order from the highest to lowest priority, is below:

1. What is the relative effectiveness of available procedural treatments (e.g., hysterectomy, myomectomy, uterine artery embolization (UAE), magnetic resonance image-guided focused ultrasound, endometrial ablation) on durability of symptom relief and patient reported outcomes?
2. What is the relative effectiveness of available procedural versus nonprocedural (medical) treatments as initial therapy on durability of symptom relief and patient reported outcomes?
3. What are the characteristics of validated and reliable classification systems of standard anatomic staging to use in research and clinical care of women with uterine fibroids?
4. What are the characteristics of validated and reliable classification systems of patient-reported outcomes (including patient preferences, disease-specific and general quality of life, and patient satisfaction) to use in research and clinical care of women with uterine fibroids?
5. What are the characteristics of validated and reliable classification systems of measures of responses to specific symptoms (such as menstrual pictograms, menstrual diaries, hemoglobin) to use in research and clinical care of women with uterine fibroids?
6. Are there genotypes, gene mutations, gene/environment interactions, epigenetic modifications, or other biomarkers that differ by race or ethnic group that may account for differences in the incidence of disease, natural history, and treatment response (including rate of growth and symptom patterns) among these groups?
7. What is the natural history of uterine fibroids in terms of fibroid growth, regression, and symptomatology among women who choose watchful waiting over durations longer than 6 months? What factors including age, race/ethnicity, smoking status, reproductive history, history of contraceptive use, body mass, family history, and menopausal status affect the natural history of disease?
8. What are the most effective dissemination approaches for providing patients and providers with the best evidence on fibroid management, and do these vary across different subpopulations?
9. What individual strategies (e.g., watchful waiting, lifestyle changes) or combinations (including different sequencing) of strategies are most frequently used as treatment in fibroid management? How does this vary by patient characteristics (childbearing aim, age, language, demographics, insurance status, provider characteristics, patient preference, social/cultural factors, and geography)?
10. What are the incidence, prevalence, and burden of disease (accounting for misclassification of symptoms) of fibroids in the United States?

11. How do patients and providers currently identify and choose strategies for fibroid management (including acquisition and processing of available information and patient-provider communication)?
12. How do different strategies for shared decisionmaking affect outcomes, especially patient-reported outcomes?
13. What methods of coordinating care among different providers are most effective in improving outcomes?

Study Designs for Research Priorities

The prioritized research questions constitute a very important, stakeholder-driven research agenda for the field of uterine fibroid disease. These questions address the areas of relative effectiveness, methods, natural history, patterns of use, genetics, and care coordination and shared decisionmaking. The questions cover gaps across the research life cycle, from foundational research to dissemination and translation strategies. Answering these questions will contribute significantly to understanding the causes, progression, and management of uterine fibroid disease. The development of studies to address these questions should begin with a formal design process for each question or question area. The formal design process starts with discussions of potential research challenges with stakeholders, reviews of the literature and other sources, such as ClinicalTrials.gov, to identify ongoing research projects, and potentially the use of existing data sources to provide information to inform the study design or to assess the study feasibility. Using the information gained in these first steps, the protocol development team can assess study design options, define the study objectives, determine the setting and participants, design the data collection plan, and develop the statistical analysis plan. Formal review with stakeholders and clinical experts is then necessary to refine and revise the protocol before launching the study.

This design process is being used to develop the research protocol for the two relative effectiveness questions identified by stakeholders as the highest research priority. The project team has completed the first two phases of the design process and is now circulating the protocol for review and discussion. The objectives of the planned study are: (1) to evaluate the effectiveness of different treatment pathways in achieving relief from symptoms of uterine fibroids and overall quality of life, with a focus on (a) comparison of hysterectomy as first procedural treatment to uterine sparing procedural treatments, and (b) comparison of all procedural treatments to nonprocedural (medical) treatments; and (2) to describe the pathways of management and treatment for symptomatic uterine fibroids of greater than 6 months duration among women who have tried and "failed" at least one medical treatment. By meeting these objectives, the study aims to generate new evidence that may assist decisionmakers (patients, providers, and payers) in selecting therapies and management strategies that will meet both the patients' therapeutic aims and reproductive goals. The ultimate goal of the study is to support improved treatment decisions, leading to better clinical management and enhanced quality of life for patients with uterine fibroid disease.

In selecting a study design option, the project team considered several factors. First, the difficulties with randomization raised during the Stakeholder Committee meeting were reviewed. At the meeting, stakeholders, including patient representatives, noted the importance of studying hysterectomy, but also emphasized that hysterectomy is a treatment of last resort for most patients, and that patients would be reluctant to participate in a randomized study that included hysterectomy as an option. Second, the team reviewed the findings from the preliminary data

analyses conducted for this project. The data analyses produced descriptive profiles of patient populations with a uterine fibroid diagnosis, using data from the National Inpatient Sample, the State Ambulatory Surgery database, and the Medicaid program. While the data analyses provided valuable insights into variation in treatment patterns, they also highlighted the limitations of retrospective data analyses, including an inability to adjust data to reflect disease severity or other potential confounders and difficulty in determining initial treatment choices. The project team's investigations into additional retrospective data analyses using electronic health record (EHR) data or integrated health system databases revealed limitations of those sources as well. For example, the utility of EHRs or paper medical records is limited because key clinical and outcomes data (e.g. patient-reported outcomes (PRO) data) are not widely collected or coded. Data sets from integrated health systems, where both claims and medical records may be available, also generally lacks complete baseline data and PRO data. In addition, even some large health systems are likely not to be nationally representative. Due to these factors, the study is planned as a prospective, longitudinal, observational cohort study.

This study design offers several potential benefits as well as some limitations. First, the observational nature of the design will allow the study to have broad inclusion criteria and minimal exclusion criteria. The study will also enroll patients from a diverse group of study sites, with the goal of producing results that will be generalizable to a wide range of uterine fibroid disease patients who present to a variety of practice settings nationwide. By leaving treatment decisions up to the patient and provider (and not randomizing patients to a particular treatment protocol), the study may include a larger percentage of eligible patients than would be likely with a randomized design. The longitudinal design also allows for long-term (5-year) followup with patients. Unlike retrospective studies, which are limited by the availability of existing data, the prospective nature of the design will allow the study to collect detailed clinical and outcomes data, including PROs. Limitations of the study design may include confounding by indication, where differences that are observed between treatment groups reflect differences in the patients who chose that treatment option, rather than differences in the effectiveness of the treatment. For example, confounding may occur if patients with a less severe form of the disease typically select treatment A, while patients with a more severe form select treatment B. Treatment A may appear to be more effective, but this may be due to the differences in disease severity in patients selecting that treatment. In this study, efforts will be made to collect data on all known predictors of treatment decision and response to therapy (e.g., disease severity, age, reproductive aim) and to include these predictive variables in multivariate statistical analyses to minimize the potential effects of confounding by indication. A summary of the protocol is included in the "Next Steps" section below.

While completing the formal design process for the other 11 prioritized research questions is not within the scope of this project, it is possible to highlight some considerations for each research topic area, based on the project team's literature review and discussions with stakeholders. These considerations are summarized below, by research topic area:

Methods

These three questions address the need for new tools for an anatomic staging system, PROs, and measures of response to specific symptoms. The current lack of effective tools in these areas hinders efforts to conduct new research in uterine fibroid disease. For example, the lack of a standard scoring system creates ambiguity in the classification and description of uterine fibroids, making it difficult to stratify patients by disease severity or type in clinical studies. New PROs and measures of response to symptoms are needed for accurate assessments

of treatment effectiveness. Addressing these questions will require a multistep approach that includes the development, testing, and validation of new tools. The development of new methods may facilitate research in other areas of uterine fibroid disease.

Natural History

The two questions on natural history aim to increase understanding of the disease, including incidence, prevalence, progression, symptoms, and variations among patients. Currently, the incidence and prevalence of uterine fibroids in the general population are unclear. The existing research in this area either included small samples of patients or focused on subgroups of patients. The natural history of uterine fibroid disease is also not well documented. An improved understanding of the natural history of the disease could help women to better understand the likely course of the disease and make more informed treatment decisions. This research may also facilitate studies of the genetic basis for the disease. New research in this area will likely require large, long-term studies, possibly of an observational design. Two key challenges for studies in this area are the large scope and the need for a standardized approach to confirming and classifying fibroids, including asymptomatic fibroids.

Patterns of Use

This question aims to increase understanding of current treatment patterns for uterine fibroid disease. Little is known about current treatment patterns, including what combinations or sequences of treatment are most frequently used and how these patterns vary by patient characteristics. Increased knowledge in this area could support better study designs for other questions and provide information to use when designing dissemination and translation strategies. The current lack of information in this area is largely due to the difficulty of using existing data sources to answer this question. A small number of prospective studies exist, but they were primarily conducted in academic medical centers and therefore may not represent patterns of care in the broader population.[54] New data collection efforts are likely to be necessary to address this question and could potentially take the form of observational studies, cross-sectional studies, or surveys.

Genetics

This question addresses the fundamental lack of information on the genetic basis for uterine fibroid disease. The goal of addressing this question is to develop evidence that may both improve treatment decisions and facilitate the development of new treatments. For example, knowledge of the genetic determinants of the timing and severity of disease may enable patients to better understand the likely outcomes of management strategies based on their individual status. This research may also identify new pathways for treatment or potential strategies for prevention. To date, some basic research has been done in the area of gene mutations, and the Brigham and Women's Hospital Center for Uterine Fibroids recently launched a tissue bank initiative. However, little to no research has been done in genotypes, gene/environment interactions, epigenetic modifications, or other biomarkers. New research in this area will require the collection of biosamples and may need to study large samples of women to account for variations in disease progression, symptoms, and response to treatment. Additional research into the natural history of the disease may also be necessary to inform research in this area.

Care Coordination and Shared Decisionmaking

The four questions related to care coordination and shared decisionmaking are designed to address issues related to the amount and type of information being provided to patients to

support treatment decisions. During the Stakeholder Committee meeting, patient representatives noted that they received very different information on treatment options from providers. The goal of care coordination and shared decision is to improve flow of information from providers to patients and to assist providers and patients in engaging in substantive dialogue about treatment choices. New research in this area will require more information on current treatment patterns and the relative effectiveness of available treatments. Without new information in these areas, it is difficult to develop better methods of coordinating care and improving patient decisionmaking. The development of better methods will be particularly important to shape the strategies used to disseminate the findings from other studies.

Governance Structures for Research Priorities

The purpose of a governance structure is to ensure that a study is conducted with transparency in operations, decisionmaking, and reporting of results. The principles of governance for observational studies can be adapted from those included in the *Registries for Evaluating Patient Outcomes: A User's Guide*.[55] Some general recommendations for governance structures are listed below:

- Involve a broad group of stakeholders. Both stakeholders who are directly affected by the study findings and those who are not directly affected should be included.
- Codify all aspects of the governance plan in written format.
- Establish an executive or steering committee with clear responsibility for the major financial, legal, ethical, scientific, and administrative decisions related to the study.
- Consider establishing additional committees, such as scientific or data access committees, to oversee specific aspects of the study in consultation with the executive or steering committee.

The protocol being developed as part of this project describes a governance structure. In this governance structure, study oversight, and administration will be provided by four groups: the Stakeholder Committee, the Technical Working Group, the Data Access and Publications Committee, and the Study Coordinating Center. The distinct role of each group is described below:

Stakeholder Committee

Recognizing the importance of broad input from decisionmakers (including patients, providers, and payers) in comparative effectiveness research, this study will establish a large Stakeholder Committee. The Stakeholder Committee will include 20 to 30 representatives of various stakeholder groups, including patient advocacy groups, consumer groups, providers, researchers, and payers. The Committee will provide high-level guidance on the types of analyses that are important to stakeholders and on opportunities for dissemination and translation of study findings. It is anticipated that the Committee will meet in person at least three times during the 5-year duration of the study (e.g., during the planning phase, after interim analyses are complete, and after the study has ended). The Committee may hold additional meetings by conference call. Members of the Committee may also be consulted on an ad-hoc basis to discuss specific questions.

Technical Working Group

The Technical Working Group (TWG) will oversee the scientific conduct of the study and provide guidance on study design, implementation, operations, and analyses. The TWG will be comprised of five to seven clinical experts and methodologists (e.g., epidemiologists, statisticians) with experience in the conduct of observational clinical research in uterine fibroid disease. At least some of the TWG Committee members will be investigators enrolling patients in this study. Select Technical Working Group members will be investigators enrolling patients in this study. All members of the TWG will also be members of the broader Stakeholder Committee. Members of the TWG will be involved for the entire duration of the study. In early phases, members will review documents, such as the protocol and the case report forms. During study operation, members will address practical issues (e.g., patient recruitment and barriers to followup) and consider interim analyses. At the close of the study data collection, members will provide support for analysis and interpretation of the data. It is anticipated that members will meet in person at least once a year and by conference call as needed. The specific activities of the TWG will be codified within a committee charter.

Data Access and Publications Committee

A subset of members of the Technical Working Group, together with some additional representatives of the study investigators, will form the Data Access and Publications Committee (DAPC). The DAPC will be responsible for reviewing research requests. All individual investigators will have access to data from their own site. Requests to access aggregate data from the entire study, either from investigators who are participating in the study or outside investigators, will be directed to the DAPC. It is anticipated that first preference will be given to participating investigators and collaborators. The DAPC will be responsible for reviewing these requests to ensure that there is no duplication of effort among physicians and for consistency with established policies. Researchers who wish to use study data for research, publications, or presentations will present a brief proposal to the DAPC in the form of a plan that describes the research objectives and data requirements. The DAPC will review the request to determine feasibility and appropriateness. The DAPC may also review manuscripts or abstracts prior to submission to provide additional guidance.

Study Coordinating Center

The Study Coordinating Center (SCC) will be responsible for the day-to-day study management and administration. The SCC will manage site contracting and IRB support, oversee data collection, data management, and analysis activities, and support analysis and reporting efforts. The SCC will consult with the Technical Working Group as needed to resolve clinical or logistical issues that arise during the conduct of the study. The SCC will also be responsible for coordinating the activities of the Stakeholder Committee, Technical Working Group, and DAPC (e.g., meeting scheduling and logistics, coordination of document review).

While this governance structure is appropriate for the proposed prospective, observational study, other types of studies will require different governance structures. In general, the nature of the study will determine the appropriate governance structure. For example, retrospective studies of de-identified claims data may require less planning related to protecting patient privacy. Studies that conduct long-term followup directly with patients have very different concerns related to patient privacy and data security. Studies that collect data on specific marketed products may need to address adverse event reporting in their governance and study planning, whereas surveys to understand factors that drive treatment choice are unlikely to

encounter this issue. Addressing the prioritized research questions described above will likely require multiple study designs and various governance structures.

In addition to governance structure, studies should develop governance plans to address other issues, such as ownership of data. For example, in some studies, individual study sites retain ownership of their own data, while the study sponsor owns the aggregate study data. These points are important to clarify in contracts with study investigators and in the formal governance plans. Procedures for managing conflicts of interest should also be documented in the governance plan.

Cost Estimates for Research Priorities

Similar to the governance structures, the costs estimates for addressing the components of the prioritized research agenda will vary widely depending on the research approaches that are used. For example, a retrospective study using data from an integrated health system to examine treatment patterns may be less expensive than a large, long-term observational study to describe the natural history of the disease. Factors such as the number of patients enrolled, the length of followup, the scope of data collection, and the need to collect biospecimens all influence cost. With respect to the study currently being designed, costs are estimated to be in the $7 million to $12 million range, depending on how study parameters and sample size may change during protocol finalization.

Next Steps

Protocol Development

Following the Stakeholder Committee meeting, the project team developed a protocol and data analysis plan to address the highest priority questions identified by the stakeholders. The Study Concept table below summarizes the project team's preliminary work in developing the protocol. It should be noted that during the in-person Stakeholder Committee meeting, a preliminary study design using the categories and listings shown in Table 4 was developed after the research question prioritization. It was then presented to the group and initial feedback was obtained. This information formed the basis for developing the draft protocol. The section that follows Table 4 describes the plans for using additional data sources to inform the protocol.

The protocol and data analysis plans are currently under review with the Stakeholder Committee and other expert reviewers. Following review, the protocol and data analysis plan will be revised and finalized.

Table 4. Study concept

Project Title	***Research on the Comparative Management of Uterine Fibroids***
Research objective(s)	The primary objectives of the study are: 1. To evaluate the effectiveness of different treatment pathways in achieving relief from symptoms of uterine fibroids and overall quality of life, with a focus on: a. comparison of hysterectomy as first procedural treatment to uterine sparing procedural treatments b. comparison of all procedural treatments to nonprocedural (medical) treatments 2. To describe the pathways of management and treatment for symptomatic uterine fibroids of greater than 6 months duration, among women who have tried and "failed" at least one medical treatment including: a. treatment sequencing b. durability of response The secondary objectives of the study are: 1. To evaluate relief from symptoms of uterine fibroids and overall quality of life by reporting the effectiveness of initial management by specific individual treatments. 2. To evaluate reproductive outcomes by specific individual treatments among women of childbearing potential.
Primary outcome variable(s)	The primary outcomes of interest will be symptom relief and quality of life, as reported by patients through validated instruments. The Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL) and the RAND 36-Item Health Survey 1.0 (or other general health measure) will be used.

Table 4. Study concept (continued)

Project Title	Research on the Comparative Management of Uterine Fibroid Disease
Other variables	Secondary outcomes of interest include reproductive outcomes among women of childbearing potential. Complications associated with individual treatments will be assessed. The data elements will include the following items: patient demographics, reproductive history, gynecologic history, stage and severity of uterine fibroids (Bethesda system or other assessment method to be determined), therapeutic goals, reproductive aim (optimize fertility, preserve fertility, not interested in preserving fertility or postmenopausal or surgically sterilized), patient self-report of symptoms using validated measure(s), patient self-report of quality of life using validated measure(s), initial and subsequent courses of treatment for uterine fibroid disease, alternative treatments for uterine fibroid disease, adverse events, reproductive outcomes.
Study design	Prospective, observational cohort study
Participants and setting	The study will enroll women ages 18 and over with symptomatic uterine fibroid disease of greater than 6 months' duration, who have failed at least one medical treatment, at the time of initiation of a first procedural treatment or new nonprocedural treatment. The study will aim to enroll sites representative of uterine fibroid care in the United States. This will include practices representative of different strategies by geography, practice type, and practice size.
Data source(s) or database name(s)	The study will use case report forms (CRFs) to collect data. The specific data elements to be included in the study will be tested and assessed for feasibility using other data sources (e.g., electronic health record data or claims data). The study will offer patient-facing forms in both English and Spanish languages and will offer direct followup with patients (through a central registry coordinating center) to maximize patient retention and completion of patient-reported outcomes (PROs).
Generalizability of findings	In the planned prospective cohort study, eligible subjects will be enrolled systematically into each treatment comparison group, and treatment decisions will reflect real-world medical decisionmaking for typical patients. The generalizability of the findings should be reflective of the broad inclusion and minimal exclusion criteria, with the study population expected to be representative of uterine fibroid patients seen in practices similar to those participating in the study.
Techniques to minimize bias	Enrollment bias: Sites will be required to maintain screening logs of all patients meeting eligibility criteria. The screening logs should match to other sources of data. A random chart audit will be conducted on uterine fibroid patients identified through billing records (which do not contain clinical data) who are not included in the screening log to determine if they meet the primary eligibility criteria. Such an audit will be performed "for cause" for any site that has a lower than expected rate of study eligible patients as a percentage of total patient volume relative to other participating sites. Channeling bias: Proposed method of addressing bias in the selection of therapies is discussed under statistical methods below. Inconsistent interpretation of CRFs by participating centers: All centers/sites will undergo standardized training and utilize standardized documentation for completing of CRFs at enrollment and for each followup assessment. Followup bias: Based on the literature from other registries, a loss to followup rate of at least 15 percent by 12 months is anticipated. The study may be able to obtain a lower loss-to-followup rate by using a number of methods, such as organizing a central followup center or facility or obtaining secondary contact information for patients.

Table 4. Study concept (continued)

Project Title	**Research on the Comparative Management of Uterine Fibroid Disease**
Estimated sample size for each research objective	The target number of subjects is 1,141 subjects for the medical therapy group, and half that or 571 each for the hysterectomy and uterine sparing procedures groups, for a total of 2,282 subjects for the study.
Statistical methods	Primary Analysis: The proportion of patients with clinical "success" defined as symptom relief measured by a 10 point reduction in the Symptom Severity Scale (SSS) of the UFS-QOL at the 1-year followup between initiated treatment groups as determined at the time of enrollment will be reported for the comparison groups. Logistic regression models will be used to adjust the treatment comparisons for key baseline covariates.
Will sensitivity analyses be conducted?	☒ YES ☐ NO
Study limitations and threats to validity	Confounding by indication is likely to be a concern. Observed differences in response according to treatment group may be reflective of differences in effectiveness of the initiated treatment modality, but may also reflect differences in the patients who choose or are chosen to receive one treatment rather than another. Efforts will be made to measure all known predictors of treatment decision and response to therapy, and to include key predictive variables in multivariate analysis to minimize bias. Residual confounding by unmeasured factors always remains a concern. Subjects "crossing over" to receive additional treatment modalities will be considered in the context of the primary "intent-to-treat" comparison as part of the real-world experience of subjects following the initial treatment rather than as a confounding factor. Given that uterine artery embolization has only recently been covered by major U.S. insurers, and that focused ultrasound remains not covered as a routine treatment by most insurance plans, ability to reach enrollment targets for these therapy groups and the representativeness of women included will be of additional concern. As for other therapies, differences in women who initiate these treatments will be compared at baseline and adjusted for in comparisons of individual treatments and treatment groups.

Use of Additional Data Sources To Inform Protocol Development

The use of additional data sources could potentially strengthen the protocol and improve the likelihood of success. The primary potential uses for such data are: (1) to define current practice in terms of the most common treatment sequences observed and refine outcomes to be measured, and (2) to evaluate existing medical records for the availability and consistency of the data elements that are intended to be collected in the protocol. The first use will help define both the initial treatment decisions and identify potential complexities that may arise from different treatment sequences (e.g., the more common sequences, the time interval between primary and secondary treatments). It will also provide insight into the variables that may need to be collected upfront for appropriate propensity scoring. The second use provides insight into both feasibility and burden. Data that are routinely collected in clinical practice are easier to standardize and collect in prospective research than new data types, even with training. Further, data that are already collected consistently in medical records can potentially be abstracted by nonphysician staff, which lowers site burden and speeds study completion.

While the preliminary data analyses provided important information on current treatment patterns, there are limitations to the generalizability of these findings, based on both the content and the populations included. Analyses of additional datasets from privately insured patients would further delineate observed treatment patterns, progression of treatments over time, intervals between significant procedures or treatments, and safety outcomes or complications. As described above, another potentially important data type for review is the medical record. While this could involve chart reviews, conducting chart reviews of paper medical records from different clinical settings with variable quality of data integrity and reporting are not cost nor time efficient.

Alternatively, electronic health records (EHRs) data could be used for this purpose and are available through several large EHRs. These data also have limitations, including lack of standardized definitions for certain endpoints and potentially nonrepresentative practice sampling. A third option, not described above, would be to obtain EHR and claims data from health systems that maintain integrated data systems. The advantage of this approach is that the longitudinal information will be more complete for the analysis of treatment patterns, and these data can also be used to assess feasibility. A disadvantage is that such data would be from a limited number of organizations that maintain both data types and can link them, and such organizations might not be generalizable to all U.S. clinical practice, settings, and locations.

A summary of the strengths and limitations of these data sources is provided in Table 5 below:

Table 5. Strengths and limitations of proposed data sources

Data Source	Proposed Use	Strengths	Limitations
Private insurer claims databases	Examine treatment patterns, geographic variation in practice patterns, other outcomes of interest	May include longitudinal data on many women. May provide information on treatment progression over time.	Unlikely to include key covariates, such as race/ethnicity or BMI. Difficult to confirm initial treatment. Does not include treatments not covered by plan.
EHR databases	Assess feasibility of collecting key data elements	Ability to assess standard data collection practices at large number of sites.	May not provide integrated picture of patient care. May not include longitudinal data on care patterns. May be limited to specific provider systems.
Integrated data (EHR, claims)	Examine treatment patterns, assess feasibility of collecting key data elements	May include more complete longitudinal data than claims data alone. Can also be used to assess standard data collection practices.	Limited to specific organizations that maintain both types of data and can link them. May not be representative of U.S. practice.

After discussion with several possible data sources, the project team selected an EHR database and an integrated database for further retrospective data analyses. These data sources were selected to promote understanding of patterns of care for uterine fibroid disease patients, provide information on comorbidities and predictors of patient care, and assess the feasibility of the proposed data collection. Both data sources are equipped to provide a clinically rich longitudinal picture of uterine fibroid patient care. These data sources can also examine patient treatment by age, race, body mass index, smoking status, and other important patient-level demographic and clinical variables relevant to uterine fibroid disease patients. The EHR database, while limited to ambulatory records, has approximately fifteen million patients across

43 states represented in its data. This representative sample of the U.S. population will provide detailed patient profiles of a large population of women with uterine fibroid disease. The integrated database, while restricted to patients in the northeastern United States, will be able to provide a picture of patient care across multiple settings. By using both data sources, the project team hopes to obtain a clearer picture of current treatment patterns for uterine fibroid disease.

The findings from these additional data analyses will be incorporated during the protocol revision phase of the project.

Conclusions

This project offered a unique opportunity to involve stakeholders in setting a research agenda for the treatment and management of uterine fibroids. The stakeholders, organized into a small Technical Working Group and larger Stakeholder Committee, provided guidance on developing the initial list of 64 research questions, revising and narrowing the list to 12 questions, and prioritizing the final questions. The stakeholders included patient, consumer, clinician, insurer, and Federal agency representatives. The inclusion of multiple stakeholder groups established a balanced approach to the selection of research priorities. Through transparent interaction with a broad and inclusive Stakeholder Committee, the project attempted to overcome a major flaw in the current clinical research enterprise: the tendency for researchers to become disconnected from the practical needs of patients and clinicians. The result of this process is a prioritized research agenda that should reflect the needs of those making decisions related to the treatment and management of uterine fibroids. This paper documents the strengths and limitations of this approach to priority setting and stakeholder engagement and may help to guide similar efforts in the future.

The next phase in this project is the development of a research protocol and data analysis plan to address the highest priority research questions. The project team has developed the draft protocol and data analysis plan and is now circulating it to the Stakeholder Committee and other experts for review. Following the review period, the study protocol will be revised in consultation with the Committee and AHRQ. In addition, the findings from feasibility assessments and additional data analyses will be used to refine the protocol. After the protocol has been finalized, the project team will engage the Stakeholder Committee and AHRQ resources such as the Eisenberg Center in dissemination activities. A dissemination plan will be developed in the coming months and implemented once the protocol has been finalized.

References

1. Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.
2. Viswanathan M, Hartmann K, McKoy N, et al. Management of Uterine Fibroids: An Update of the Evidence. Evidence Report/Technology Assessment No. 154 (Prepared by RTI International–University of North Carolina Evidence- based Practice Center under Contract No. 290-02-0016. AHRQ Publication No. 07-E011. Rockville, MD: Agency for Healthcare Research and Quality. July 2007.
3. Stewart EA. Uterine Fibroids. Lancet 2001 Jan;257(9252):293-298.
4. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003 Jan;188(1):100-107.
5. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990;94:435-438.
6. Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.
7. Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.
8. National Institute of Child Health and Human Development (NICHD), Public Information and Communications Branch. Uterine Fibroids, 2003. Available at: http://www.nichd.nih.gov/publications/pubs/fibroids/index.htm.
9. Viswanathan M, Hartmann K, McKoy N, et al. Management of Uterine Fibroids: An Update of the Evidence. Evidence Report/Technology Assessment No. 154 (Prepared by RTI International–University of North Carolina Evidence- based Practice Center under Contract No. 290-02-0016. AHRQ Publication No. 07-E011. Rockville, MD: Agency for Healthcare Research and Quality. July 2007.
10. Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.
11. Carls GS, Lee DW, Ozminkowski RJ, et al. What are the total costs of surgical treatment for uterine fibroids? J Womens Health 2008;17(7):1119-1132.
12. Stewart EA. Uterine Fibroids. Lancet 2001 Jan;257(9252):293-298.
13. Whiteman MK, Hillis SD, Jamieson DJ, et al. Inpatient hysterectomy surveillance in the United States, 2000–2004. Am J Obstet Gynecol 2008;198(1):34.e1–34.e7.
14. Whiteman MK, Hillis SD, Jamieson DJ, et al. Inpatient hysterectomy surveillance in the United States, 2000–2004. Am J Obstet Gynecol 2008;198(1):34.e1–34.e7.
15. Hirst A, Dutton S, Wu O, et al. A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study. Health Technol Assess 2008;12(5):1-248.
16. Liu JP, Yang H, Xia Y, et al. Herbal preparations for uterine fibroids. Cochrane Database Syst Rev 2009 Apr;15(2):CD005292.

17. Viswanathan M, Hartmann K, McKoy N, et al. Management of Uterine Fibroids: An Update of the Evidence. Evidence Report/Technology Assessment No. 154 (Prepared by RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016. AHRQ Publication No. 07-E011. Rockville, MD: Agency for Healthcare Research and Quality. July 2007.

18. Myers ER, Barber MW, Couchman GM, et al. Management of Uterine Fibroids—Volume 1. Evidence Report; Volume 2. Tables and Bibliography. Rockville, MD: Agency for Healthcare Research and Quality, 2001.

19. Liu JP, Yang H, Xia Y, et al. Herbal preparations for uterine fibroids. Cochrane Database Syst Rev 2009 Apr;15(2):CD005292.

20. Ke LQ, Yang K, Li J, et al. Danazol for uterine fibroids. Cochrane Database Syst Rev 2009 Jul;8(3):CD007692.

21. Rolnick SJ, Flores SK, Fowler SE, et al. Conducting randomized, controlled trials. Experience with the dysfunctional uterine bleeding intervention trial. J Reprod Med 2001 Jan;46(1):1-5, discussion 5-6.

22. Varner RE, Ireland CC, Summitt Jr RL, et al. Medicine or Surgery (Ms): a randomized clinical trial comparing hysterectomy and medical treatment in premenopausal women with abnormal uterine bleeding. Control Clin Trials 2004 Feb;25(1):104-118.

23. Myers ER, Steege JF. Risk adjustment for complications of hysterectomy: utility of routinely collected administrative data. Am J Obstet Gynecol 1999; 181:567-575.

24. Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.

25. Tunis S, Seidenfeld J. Evidence making: Developing tools and strategies for comparative effectiveness. Asian Hospital & Healthcare Management 2009;19:11-16.

26. Committee on Comparative Effectiveness Research Prioritization. Initial National Priorities for Comparative Effectiveness Research. Washington, DC: Institute of Medicine. 2009.

27. Chalkidou K, Whicher D, Kary W, et al. Comparative effectiveness research priorities: Identifying critical gaps in evidence for clinical and health policy decision-making. Int J Technol Assess Health Care 2009;25(3):241-248.

28. Chalkidou K, Whicher D, Kary W, et al. Comparative effectiveness research priorities: Identifying critical gaps in evidence for clinical and health policy decision-making. Int J Technol Assess Health Care 2009;25(3):241-248.

29. Viswanathan M, Hartmann K, McKoy N, et al. Management of Uterine Fibroids: An Update of the Evidence. Evidence Report/Technology Assessment No. 154 (Prepared by RTI International–University of North Carolina Evidence- based Practice Center under Contract No. 290-02-0016. AHRQ Publication No. 07-E011.Rockville, MD: Agency for Healthcare Research and Quality. July 2007.

30. Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.

31. McKenna HP. The Delphi technique: a worthwhile research approach for nursing? J Adv Nurs 1994;19(6):1221-1225.

32. Henschke N, Maher CG, Refshauge KM, et al. Low back pain research priorities: a survey of primary care practitioners. BMC Family Practice 2007;8:40.

33. Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.

34. Viswanathan M, Hartmann K, McKoy N, et al. Management of Uterine Fibroids: An Update of the Evidence. Evidence Report/Technology Assessment No. 154 (Prepared by RTI International–University of North Carolina Evidence- based Practice Center under Contract No. 290-02-0016. AHRQ Publication No. 07-E011.Rockville, MD: Agency for Healthcare Research and Quality. July 2007.

35. Liu JP, Yang H, Xia Y, et al. Herbal preparations for uterine fibroids. Cochrane Database Syst Rev 2009 Apr;15(2):CD005292.

36. Ke LQ, Yang K, Li J, et al. Danazol for uterine fibroids. Cochrane Database Syst Rev 2009 Jul;8(3):CD007692.

37. Harding G, Coyne KS, Thompson CL, et al. The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). Health Qual Life Outcomes 2008 Nov 12;6:99.

38. Hirst A, Dutton S, Wu O, et al. A multi-centre retrospective cohort study comparing the efficacy, safety and costeffectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study. Health Technol Assess 2008;12(5):1-248.

39. O'Sullivan AK, Thompson D, Chu P. Cost-effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids. International J of Tech Assessment In Health Care 2009;25:14-25.

40. Carls GS, Lee DW, Ozminkowski RJ, et al. What are the Total Costs of Surgical Treatment for Uterine Fibroids. J Women's Health 2009;17:1119-1132.

41. Whitlock EP, Lopez SA, Chang S, et al. Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the Effective Health Care program. J Clinical Epidemiology 2009 June.

42. The Federal Coordinating Council for Comparative Effectiveness Research—Report to the President and the Congress. June 2009. Available at: http://www.hhs.gov/recovery/programs/cer/cerannualrpt.pdf.

43. Kary W, Bergthold L, Talbott M, et al. Issue Brief: Coverage for Evidence Development: A Conceptual Framework. Baltimore, MD: Center for Medical Technology Policy. January 2009.

44. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstetrics and Gynecology 1993;82:(5):736–740.

45. Davis JB, Broder MS, Catherino WH, et al. Development of an evidence-based classification system for uterine fibroids: Poster session 1. Fertility and Sterility 2009;92(3):S128.

46. Harding G, Coyne KS, Thompson CL, et al. The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). Health and Quality of Life Outcomes 2008;6(1):99.

47. Peddada SD, Laughlin SK, Miner K, et al. Growth of uterine leiomyomata among premenopausal black and white women. Proceedings of the National Academy of Sciences 2008 Dec 16;105(50):19887-19892.

48. Baird DD, Dunson DB, Hill MC, et al. High Cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obset Gynecol 2003 Jan;188(1):100-107.

49. Wise LA, Palmer JR, Harlow BL, et al. Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: prospective study. Am J Epidemiogl 2004 Jan 15;159(2):113-123.

50. McDonald KM, Sundaram V, Bravata DM, et al. Care Coordination. Vol 7 of: Shojania KG, McDonald KM, Wachter RM, et al., eds. Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies. Technical Review 9 (Prepared by the Stanford University-UCSF Evidence-based Practice Center under contract 290-02-0017). AHRQ Publication No. 04(07)-0051-7. Rockville, MD: Agency for Healthcare Research and Quality. June 2007.

51. Agency for Healthcare Research and Quality. The CAHPS Improvement Guide: Practical Strategies for Improving Patient Care Experience. Available at: http://www.cahps.ahrq.gov/QIGuide/content/interventions/SharedDecisionMaking.aspx. Accessed January 28, 2010.

52. Perlis RH, Delbello MP, Miyahara S, et al. Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I systematic treatment enhancement program for bipolar disorder participants. Biol Psychiatry 2005 Oct 1;58(7):549-553

53. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. December 2009.

54. Viswanathan M, Hartmann K, McKoy N, et al. Management of Uterine Fibroids: An Update of the Evidence. Evidence Report/Technology Assessment No. 154 (Prepared by RTI International–University of North Carolina Evidence- based Practice Center under Contract No. 290-02-0016. AHRQ Publication No. 07-E011. Rockville, MD: Agency for Healthcare Research and Quality. July 2007.

55. Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide 2nd Edition. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. dba Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No. 10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010.

Appendix A. Preliminary Data Analysis Findings

The data analyses consisted of descriptive profiles of patient populations with a uterine fibroid diagnosis. The following data sources were used to look at different aspects of disease treatment and complications.

National Inpatient Sample (NIS) calendar year (CY) 2007. The NIS is a nationally compiled inpatient episode-level database with detailed information on treatment type, comorbidities, complications of care, financing of care, and patient demographics. The study data consist of records of inpatient treatment with either uterine fibroids as a primary or secondary diagnosis or as a significant patient factor of care. For more complex uterine fibroid treatments, e.g. abdominal hysterectomy, inpatient care is the practice standard. For these procedures, the NIS includes complete information. For treatments that require less recovery monitoring, the NIS inpatient data are incomplete, since many of the procedures are conducted as ambulatory surgery with no inpatient stay. The NIS data are robust for studying patterns of care and demographics for individuals with active treatment with procedures that require inpatient recovery and monitoring.

State Ambulatory Surgery Database (SASD) CY 2007. The SASD consists of records of outpatient treatments with detailed information on treatment type, comorbidities, complications of care, financing of care, and patient demographics. The data are available from individual states. The study data included all records for outpatient care with either a primary or secondary diagnoses of uterine fibroids, from the States of California, New York, Florida, Maryland, and Wisconsin. The SASD provided insight into treatment patterns for individuals under treatment for uterine fibroids that are less complex and do not require inpatient recovery and monitoring. The data are complemented by the State Inpatient Database, which is similar to the NIS but restricted to single States. By using the SASD and the SIS, it becomes possible to look at all surgical care for uterine fibroids and to study the influence of treatment type, demographics, payer, and State on care type and care complications. The five States chosen include approximately one-third of all uterine fibroid inpatient episodes. The combined source provides detail on patients with active hospital treatments related to uterine fibroids in the study States.

National Medicaid Data CY 2001-2005. The Medicaid Analytic Extract (MAX) data are compiled by the Centers for Medicare and Medicaid Services (CMS) on an annual basis using claims and enrollment data submitted by individual State Medicaid programs. The records are patient encounter–level records of care with dates of service and patient identifiers. The study data included all Medicaid beneficiaries with a uterine fibroid diagnosis sometime in the study period. The data are limited to Medicaid beneficiaries but provide a cross-setting-of-care profile of treatment modalities, including pharmaceutical products. The study data include records of all care regardless of whether a specific service use referenced a uterine fibroid diagnosis. The scope of the data permitted analyses that provide a picture of the entire population of uterine fibroid patients, including both those with active treatments and those only under physician supervision. The analyses focused on variation in treatment type and complication rates.

Several key limitations to these analyses should be noted. First, the information presented here is descriptive in nature; data have not been adjusted to reflect differences in demographics, comorbidities, severity of uterine fibroid disease, or other potential factors that may account for

observed differences across settings and payers. Second, the NIS, SASD, and SIS data are devoid of any patient-level identifiers. Records are unique by episode of patient care but not by patient. As such, there is no way to describe patient-level patterns of care over time in these datasets or ensure that a patient is not represented more than once in the data. Fourth, while the Medicaid data can provide patient-level patterns of care over time, the Medicaid population is unlikely to be generalizable to the overall U.S. population because of the restrictive eligibility criteria for the Medicaid program.

While the above limitations demonstrate the need for further research, the descriptive analyses presented here provide valuable insight into the patient population. Description of uterine fibroid patient volume, geographic variations in care, and frequency of uterine fibroid disease–related procedures in inpatient and outpatient settings will inform the design of future studies in this area.

Major Findings of Analyses

Below are the major findings by data source.

NIS

- Abdominal hysterectomy procedures occur in 47 percent of the hospital stays with a uterine fibroid primary or secondary diagnosis.
- Removal of tubes and ovaries occur in 46 percent of hysterectomy procedures
- The complication rate in inpatient stays with a primary or secondary diagnosis of uterine fibroid disease is approximately 10 percent and includes medical and surgical—complications, fever, and urinary tract infections.
- The highest frequency payers of inpatient care are private insurance (73%) and Medicaid (11%).
- The relationship between payer and race is significant. The largest differences were found in the comparison of Medicaid to private insurance financing. Hospital episodes with Medicaid financed care were half as likely to be white (20% vs. 39%), three times as likely to be Hispanic (21% vs. 7%) and close to twice as likely to be black (31% vs. 18%).
- The two highest frequency payers exhibited varying treatment and complication patterns and different lengths of stay for hospitalizations with uterine fibroid disease as primary or secondary diagnosis. Comparing Medicaid patients to private insurance patients, Medicaid patients are younger, have higher complication rates for urinary tract infections (3% vs. 1%), longer lengths of stay (mean of 3.5 vs. 2.6 days) and lower rates of hysterectomy procedures (36% vs. 49%).

SASD/SID New York, California, Florida, Maryland, Wisconsin

- In the five study States, outpatient treatment comprised 30 percent of in-hospital care.
- The ratio of outpatient to inpatient care was highest in Maryland (43%) and lowest in California (25%).
- The most common treatment for patients with a primary or secondary diagnosis of uterine fibroid disease was abdominal hysterectomy (30%) in the combined inpatient and outpatient data.

- The rate of abdominal hysterectomy treatments varied by state and was lowest in Maryland (22%) and highest in California (32%).
- The rate of surgical complication ranged between 5percent and 6 percent in the states, fever, and urinary tract infections each ranged from 1 percent to 2 percent of the records.
- Nonabdominal hysterectomy treatment rates and care setting (outpatient to inpatient ratio) varied substantially between states. In Wisconsin 40 percent of nonabdominal high-frequency treatments were conducted in the outpatient setting; in California, the rate was 22 percent.
- Nonabdominal hysterectomy treatment types varied between states; the rate of laparoscopic hysterectomy was 7 percent in New York and 17 percent in Wisconsin. Looking at the same two states the rate for myomectomies was 18 percent in New York and 8 percent in Wisconsin.
- The two highest frequency payers were private insurance (75%) and Medicaid (11%). New York has the highest rate of Medicaid at 18 percent, California the next highest at 11 percent. The other states had a Medicaid rate of 8 percent.
- The rate of outpatient-to-inpatient care varied by payer. In the five States, 85 percent of care paid by Medicaid was for inpatient treatments, in contrast to 67 percent for private insurance.
- Holding the payer constant demonstrates strong variation in the ratio of outpatient to inpatient care by State. Looking just at private insurance financed care: myomectomies 72 percent outpatient in Wisconsin and 8 percent in California, laparoscopic hysterectomies are 60 percent outpatient in Maryland and 23 percent outpatient in Wisconsin.

Medicaid Cross-Sectional

- Cross-sectional analysis of all patients with a uterine fibroid disease diagnosis and at least 6 months of Medicaid eligibility in CY 2005.
- In total, 75 percent of Medicaid beneficiaries with an incident uterine fibroid diagnosis in the year were not subject to any of the studied surgical treatment modalities.
- The highest frequency procedure was abdominal hysterectomies, including 15 percent of the CY 2005 uterine fibroid population.
- The medical/surgical complication rate for abdominal hysterectomies was 28 percent as identified from both hospital and physician claims.
- The medical/surgical complication rate for myomectomies and nonabdominal hysterectomies was 17 percent.
- The percent of the study subjects using NSAIDs was 52 percent in the year and 22 percent for oral contraceptives.

Medicaid Longitudinal

- Longitudinal analysis of CY 2002–incident uterine fibroid cases was conducted. (Incident cases were identified based on beneficiaries with the presence of at least 12 months of Medicaid enrollment prior to the first observed primary or secondary diagnosis of uterine fibroid disease.)
- In total, 75 percent of the incident population experienced no surgical treatment in the 12 months following the first uterine fibroid diagnosis.

- The highest frequency procedure in the first 12 months following an initial uterine fibroid diagnosis was abdominal hysterectomy, at 16 percent.
- Over the followup years, oral contraceptive use dropped from 26 percent to 12 percent of the study population. NSAID use remained relatively stable over the same period changing from a 52 percent to 48 percent use rate.

Data Methods

The descriptive analyses of the population demographics and treatment patterns of uterine fibroids patients employed several different large-scale administrative data sources. Each data source provided unique opportunities to make a range of measurements of the patient population. The collection of statistics from these different sources yields insight into inpatient and outpatient care modalities and longitudinal information on clinical pathways.

For all data sources, records linked to uterine fibroid treatments were identified using the diagnosis codes in the table below.

Table A-1. Uterine fibroids study diagnosis codes

ICD9-CM	Description
218.xx	Uterine leiomyoma
219.xx	Other benign neoplasm of uterus

Three of the data sources used national and State hospital records to profile uterine treatment modalities. The hospital sources did not include patient identifiers so only services listed in the individual records were available for analysis. The third data source was a national database of Medicaid claims and enrollment data. The records included only services paid for by Medicaid. Patient identifiers were available from this source and supported patient-level analyses that spanned both setting of care and time. The data sources are listed in Table A-2 below.

Table A-2. Study data sources

Name	Year/s	Region	Patient Identifier
National Inpatient Sample (NIS)	2007	Weighted National Sample	No
State Inpatient Database (SID)	2007	5 Study States	No
State Ambulatory Surgical Database (SASD)	2007	5 Study States	No
Medicaid Analytic Extract (MAX)	2001-2005	National	Yes

For data sources with patient identifiers, the study data consisted of inpatient and outpatient hospital treatment records with either a primary or secondary diagnosis of uterine fibroids. For a data source with patient identifiers, the treatment records were used as the basis for an extraction of the complete patient history. The first data step was the identification of the treatment records, the second step used the personal identifiers on the treatment to identify and extract all claims for the patients.

National Inpatient Treatments CY 2007

The CY 2007 AHRQ National Inpatient Sample (NIS) was used to measure the frequency and types of care delivered to patient hospitalized with either a primary or secondary ICD9-CM diagnosis of uterine fibroids.

The NIS source is a compilation of records of inpatient care from state hospital discharge databases for a sample of hospitals. The NIS data are weighted (NIS *discwt* variable) to generate

regionally and nationally representative statistics. All tabulations are typically presented after the weighting factor is applied. The NIS discharge records do not include patient identifiers and can only be studied as independent events. There is no linkage between inpatient discharges for the same individual.

In total, 401,803 discharge records were selected using the study diagnosis codes. Approximately 99 percent of the study records were selected because of the uterine leiomyoma diagnosis. In total 52 percent of the selected records were observed with a uterine fibroids primary diagnosis. The tabulation of the top primary diagnosis codes in the study data is presented in Table A-3 below.

Table A-3. Top frequency primary diagnoses on NIS study records

ICD9-CM	Description	Record Count	Percent of Total
218.9	Uterine leiomyoma NOS	100,737	25%
218.1	Intramural leiomyoma	60,421	15%
626.2	Excessive menstruation	29,261	7%
218.0	Submucous leiomyoma	26,816	7%
218.2	Subserous leiomyoma	21,253	5%
617.0	Uterine endometriosis	8,104	2%
654.21	Prev c-delivery-delivrd	7,134	2%
182.0	Malig neo corpus uteri	5,853	1%
626.8	Menstrual disorder NEC	5,757	1%
220	Benign neoplasm ovary	5,312	1%
280.0	Chr blood loss anemia	4,476	1%
659.71	Abn ftl hrt rate/rhy-del	3,563	1%
620.2	Ovarian cyst NEC/NOS	3,353	1%
625.3	Dysmenorrhea	3,224	1%
618.2	Uterovag prolaps-incompl	2,928	1%
618.4	Utervaginal prolapse NOS	2,715	1%

The NIS records contain ICD-9-CM procedure codes that document the major procedures that occur in the course of the hospitalization. Since the NIS source is primarily based on claim records, information on procedures performed may not be complete. The reason is that in many cases the claim is paid based on the reason/length of the hospital stay and not for the actual medical procedures. The number of study records with no procedure code was 5 percent. The medical procedures flagged in the inpatient records are listed below in Table A-4. In total 24 percent of the records did not display any of the targeted codes in the discharge record.

Table A-4. Distribution of hospital procedures

Procedure	Record Count	Percent of Total
Myomectomy	39,028	10%
Abdominal hysterectomy	187,423	47%
Laparoscopic hysterectomy	46,070	11%
Vaginal hysterectomy	30,613	8%
Removal of tubes and ovaries	148,235	37%
Uterine artery embolization	7,363	2%
Blood transfusion	32,925	8%

The overlap between removal of tubes and ovaries and a hysterectomy procedure was 96 percent for inpatient care. Approximately 46 percent of hysterectomy procedures occurred without a removal of tubes and ovaries procedure code on the record.

The NIS record contains procedure codes and diagnosis codes that are not directly related to uterine fibroids but may be an effect of treatment or comorbidity. Table A-23 lists the

predetermined codes used to identify complications of care. Table A-5 is a tabulation of the frequency of discharge records flagged by each complication type.

Table A-5. Complications and comorbidities

Complication Type	Record Count	Percent of Total
Medical/surgical Complications	26,405	7%
Venous thrombosis/embolus	3,665	1%
Menopausal symptoms	436	0%
Dermatitis	312	0%
Nephropathy	60	0%
Wound infection	978	0%
Urinary tract infection	7,886	2%
Fever/pyrexia	6,044	2%

Nearly all NIS records listed the primary payer for the inpatient care. Table A-6 lists the distribution of reported payer type.

Table A-6. NIS financing of care tabulation

Payer	Record Count	Percent of Total
Medicaid	42,535	11%
Medicare	27,208	7%
No charge	3,762	1%
Other	16,653	4%
Private insurance	292,501	73%
Self-pay	18,043	4%
Unknown	1,101	0%

The payer is an important factor in establishing access to many services. The largest payer type is private insurance that incorporates a very wide range of benefit types and levels of provider reimbursement. The second and third most frequent payers are Medicaid and Medicare. The payer can be an important marker for at-risk populations with markedly different demographic characteristics and health needs than women with private pay insurance.

The Medicaid programs can vary from state to state in program eligibility criteria, provider reimbursement rates, and case management from state to state. Medicaid eligibility for women is based on either pregnancy, young children in the family, or a disability. Medicaid eligibility is limited to individuals with low income and the provider reimbursement rates are lower than those of other payers. The combination of lower provider reimbursements and low income is thought to inhibit access to many types of advanced care. Due to the relationship between low income and race in the United States the demographic distribution between Medicaid non-Medicaid payers can be substantial. Table A-7 documents the relationship between race/ethnicity and the source of financing of care.

Table A-7. Cross-tabulation between NIS race and financer of care

Row Labels	Medicaid	Medicare	No Charge	Other	Private Insurance	Self-Pay	Total
Asian/Pacific Isl.	2%	1%	1%	3%	3%	2%	3%
Black	31%	21%	36%	24%	18%	34%	21%
Hispanic	20%	6%	34%	13%	7%	15%	9%
Native American	1%	0%	3%	1%	0%	1%	0%
Other	3%	2%	1%	2%	2%	4%	3%
Unknown	22%	25%	6%	29%	31%	22%	29%
White	20%	44%	18%	28%	39%	22%	36%
Record count	100%	100%	100%	100%	100%	100%	100%

The racial distribution is marked with a rate of half as many white patients in Medicaid as in private insurance.

The Medicare population includes almost all elderly in the United States and adults with a physician-certified total disability. The treatments for uterine fibroids reported in the NIS are for patients 65 years of age or older are 86 percent paid by Medicare. Table A-8 shows the distribution of the financer of care by age. Table A-9 provides a cross-tabulation between treatment and financer of care.

Table A-8 Cross-tabulation between age band and financer of care

Age Category	Medicaid	Medicare	No Charge	Other	Private Insurance	Self-Pay	Total
20-34	24%	3%	11%	11%	12%	13%	13%
35-44	43%	15%	40%	40%	41%	43%	39%
45-54	27%	20%	39%	43%	40%	37%	37%
55-59	3%	4%	5%	4%	4%	4%	4%
60-64	2%	3%	4%	2%	2%	2%	2%
65-69	0%	19%	1%	0%	0%	0%	2%
70-74	0%	13%	0%	0%	0%	0%	1%
75-79	0%	10%	0%	0%	0%	0%	1%
80-84	0%	7%	0%	0%	0%	0%	0%
85+	0%	6%	0%	0%	0%	0%	0%
Record count	100%	100%	100%	100%	100%	100%	100%

The distribution of treatments in the Medicare-covered patients in contrast to other patient populations may be heavily influenced by the age imbalance. On the other end of the spectrum the Medicaid patients are on average younger than for private insurance, most likely due to eligibility rules that favor pregnant women and women with young children.

The demographic differences may be related to differences in treatment modality, complication rates, and length of stay in the hospital.

Table A-9. Cross-tabulation between treatment and financer of care

Treatment	Medicaid	Medicare	No Charge	Other	Private Insurance	Self-Pay	Total
Myomectomy	7%	3%	6%	8%	11%	7%	10%
Abdominal hysterectomy	36%	42%	41%	50%	49%	35%	47%
Laparoscopic hysterectomy	6%	10%	9%	10%	13%	5%	11%
Vaginal hysterectomy	6%	11%	8%	9%	8%	4%	8%
Removal of tubes and ovaries	25%	48%	32%	38%	38%	26%	37%
Uterine artery embolization	2%	2%	1%	1%	2%	2%	2%
Excision or destruction of lesion of uterus	7%	3%	6%	8%	11%	7%	10%
Blood transfusion	13%	9%	20%	12%	6%	23%	8%
Record count	100%	100%	100%	100%	100%	100%	100%

The treatment type is seen to vary substantially between payers as does the complication rates. Using the private insurance population as the reference is problematic due to the demographic differences observed in the Medicaid and Medicare populations. Table A-10 provides a cross-tabulation between complication rates and source of financing.

Table A-10. Cross-tabulation between complication and financer of care

Values	Medicaid	Medicare	No Charge	Other	Private Insurance	Self-Pay	Total
Medical/surgical	6%	10%	7%	7%	6%	6%	7%
Venous thrombosis/embolus	1%	2%	1%	1%	1%	1%	1%
Menopausal symptoms	0%	0%	0%	0%	0%	0%	0%
Gastritis	0%	0%	0%	0%	0%	0%	0%
Dermatitis	0%	0%	0%	0%	0%	0%	0%
Nephropathy	0%	0%	0%	0%	0%	0%	0%
Wound infection	0%	0%	0%	0%	0%	0%	0%
Urinary tract infection	3%	7%	5%	2%	1%	5%	2%
Fever/pyrexia	1%	2%	1%	2%	1%	2%	2%
Record count	100%	100%	100%	100%	100%	100%	100%

The general summary could be that Medicaid populations are less likely to receive one of the major surgical treatments, have higher rates of blood transfusions, and suffer higher rates of urinary tract infection complications than the private insurance population. The Medicare population has a higher rate of major surgery (removal of ovaries/tubes), receives more blood transfusions, and suffers a much higher surgical and urinary tract infection complication rate in comparison to the private insurance patient population. These differences in procedure types and complication rates may help explain variations in hospital lengths of stay, which are documented in Table A-11.

Table A-11 Length of inpatient stay by financing source

Payer	Mean Length of Stay (days)	Median Length of Stay (days)	Std Dev Length of Stay (days)
Medicaid	3.5	3.0	9.7
Medicare	4.0	3.0	9.4
No charge	3.2	2.0	6.4
Other	2.9	2.0	6.5
Private insurance	2.6	2.0	5.1
Self-pay	3.2	2.0	8.0
Unknown	2.9	2.0	6.8
Total	2.8	2.0	6.4

In the NIS data, private insurance patients have the shortest lengths of stay for hospitalizations with a primary or secondary diagnosis of uterine fibroid disease.

HCUP Five-State Inpatient-Outpatient Database

The NIS is compiled from State-level hospital discharge databases. A number of States in addition to their hospital discharge databases, also maintain databases of outpatient hospital and freestanding clinic surgical treatments. Five States with inpatient (SID: State Inpatient Database) and outpatient (SASD: State Ambulatory Surgery Database) databases available were chosen to create a database to compare hospital inpatient and outpatient care modalities. State-specific inpatient data were imported since the NIS is weighted to produce regional and national estimates and does not produce valid State-level statistics. The Healthcare Cost and Utilization Project (HCUP) State data do not contain person-level identifiers, so each record represents an independent observation of care (not a unique patient). Records cannot be linked to produce patient histories across the site or across time. The SASD and SID contain an unknown level of overlap in patient population. Measures of major surgery can be assumed to be unique. Procedures that can be performed multiple times may appear in both data sources leading to a double counting of patients. The totals from the sources can be accurately represented as

inpatient/outpatient hospital encounter counts. It is important to keep in mind that procedures performed in physicians' offices will not be captured in the HCUP source.

The five States chosen were: New York, California, Florida, Maryland, and Wisconsin. A total of 163,759 records were selected from the CY 2007 service period. Table A-12 below provides the distribution of patients with a primary or secondary uterine fibroids (UF) diagnosis on their hospital care record.

Table A-12. SASD/SID state distribution of treatment records

State	Ambulatory	%Ambulatory	Inpatient	%Inpatient	Total
CA	14,620	25%	44,488	75%	59,108
FL	12,762	33%	26,367	67%	39,129
MD	7,538	43%	10,068	57%	17,606
NY	11,456	30%	27,268	70%	38,724
WI	2,997	33%	6,195	67%	9,192
Total	49,373	30%	114,386	70%	163,759

Inpatient care is the highest treatment modality with 70 percent of all HCUP records; however, there is substantial variation between States. In California, 25 percent of uterine fibroid hospital records are provided as outpatient records. In contrast, in Maryland, 43 percent of records are from the outpatient hospital setting. A total 82,803, or 50 percent, of the records, are selected due to a primary diagnosis of uterine fibroids. The state variation in inpatient to outpatient care is largely maintained regardless of the primary or secondary status of the diagnosis code. It should be noted that the five state inpatient total record count is approximately one fourth of the national NIS count.

The highest frequency primary diagnoses that appear on the HCUP records are tabulated in Table A-13. The care setting is highly influenced by the primary diagnosis.

Table A-13 Top frequency primary diagnoses in 5-state study records

ICD9-CM	Description	Ambulatory	Inpatient	Total	Percent of Total Records
218.9	Uterine leiomyoma NOS	11,875	27,819	39,694	26%
218.1	Intramural leiomyoma	1,881	17,581	19,462	13%
218.0	Submucous leiomyoma	6,353	8,897	15,250	10%
626.2	Excessive menstruation	8,030	6,153	14,183	9%
218.2	Subserous leiomyoma	891	6,139	7,030	5%
617.0	Uterine endometriosis	489	2,207	2,696	2%
621.0	Polyp of corpus uteri	2,469	262	2,731	2%
626.8	Menstrual disorder NEC/NOS	2,016	1,110	3,126	2%
220	Benign neoplasm ovary	417	1,467	39,694	1%
182.0	Malig neo corpus uteri	244	1,617	1,884	1%
620.2	Ovarian cyst NEC/NOS	856	921	1,777	1%
280.0	Chr blood loss anemia	53	1,469	1,522	1%

The HCUP source contains procedure codes that can be used to identify specific treatments. The inpatient procedure codes are ICD9 codes. The ambulatory procedure codes are CPTs and HCPC codes. The ambulatory procedure codes are used for payment purposes and can be assumed to be complete and accurate. The tabulation of procedure frequency by site of care is provided in Table A-14.

Table A-14. Profile of treatments for uterine fibroids in five-state study records

Procedures	Ambulatory	Inpatient	Total	Percent of Total Records
Myomectomy	6,653	12,662	19,315	12%
Abdominal hysterectomy	292	48,836	49,128	30%
Laparoscopic hysterectomy	6,719	12,068	18,787	11%
Vaginal hysterectomy	1,019	7,979	8,998	5%
Removal of tubes and ovaries	3,295	36,887	40,182	25%
Uterine artery embolization	1,277	3,282	4,559	3%
Excision/destruction lesion of uterus	210	0	210	0%

State-level variation in procedures and complication rates, as shown in Table A-15, help to distinguish how treatment rates differ for uterine fibroid patients.

Table A-15. Rates of procedures and complications in five states inpatient and ambulatory records

	CA	FL	MD	NY	WI	Total
Procedures						
Myomectomy	9%	13%	7%	18%	8%	12%
Abdominal hysterectomy	32%	31%	22%	29%	30%	30%
Laparoscopic hysterectomy	12%	15%	10%	7%	17%	11%
Vaginal hysterectomy	7%	4%	4%	4%	15%	5%
Removal of tubes and ovaries	25%	28%	16%	23%	32%	25%
Uterine artery embolization	2%	2%	2%	6%	1%	3%
Excision or destruction of lesion of uterus	0%	0%	0%	0%	0%	0%
Blood transfusion	7%	7%	7%	8%	2%	7%
Complication						
Medical/surgical	5%	5%	5%	6%	5%	5%
Venous thrombosis/embolus	1%	1%	1%	1%	1%	1%
Menopausal symptoms	0%	0%	0%	0%	0%	0%
Gastritis	0%	0%	0%	0%	0%	0%
Dermatitis	0%	0%	0%	0%	0%	0%
Nephropathy	0%	0%	0%	0%	0%	0%
Wound infection	0%	0%	0%	0%	0%	0%
Urinary tract infection	2%	2%	2%	2%	1%	2%
Fever/pyrexia	1%	1%	1%	2%	1%	1%

The differences are substantial in choice of procedure. The choice of hysterectomy procedure type is especially sensitive to State. Differences of a factor two are observable in a number of the measurements.

The procedures that are associated with inpatient care to a high degree are abdominal and vaginal hysterectomies. Analyses of State-level variations in the site of care will not be relevant for abdominal hysterectomy, removal of tubes and ovaries and vaginal hysterectomy. Variations in site will be evident in the other procedures. In Table A-16, the site-of-care variation is examined by State for the major procedures that are observed in both inpatient and ambulatory settings of care.

Table A-16. Ratio of outpatient to inpatient care for select procedures in SID/SASD five states

State	CA		FL		MD		NY		WI	
Procedures varying by site of care	Amb.	Inp.	Amb.	Inp.	Amb.	Inp.	Amb.	Inp.	Amb.	Inp.
Myomectomy	9%	91%	54%	46%	6%	94%	41%	59%	70%	30%
Laparoscopic hysterectomy	30%	70%	46%	54%	59%	41%	21%	79%	23%	77%
Uterine artery embolization	31%	69%	65%	35%	22%	78%	10%	90%	68%	32%
Total records selected procedures	22%	78%	51%	49%	36%	64%	31%	69%	40%	60%

The table demonstrates substantial variability in inpatient care choices. For example, the site of care for myomectomies is highly variable with 91 percent inpatient care in California and 30 percent in Wisconsin. It is interesting to note that a State statistic, which is low for one procedure, may be high for another, e.g. Maryland has a low inpatient rate for laparoscopic hysterectomies but a relatively high rate of inpatient care for myomectomies.

As illustrated in Table A-17, the payer mix varies between states, especially the degree to which Medicaid finances care. The variation in Medicaid is to be expected because of differences in individual State Medicaid eligibility rules. In contrast, Medicare rates of coverage are more uniform. In all States, private insurance is by far the primary financing source. Some of the variation between States may be connected with the relative importance of Medicaid program influence.

Table A-17. SID and SASD care financing in five states

Payer	CA	FL	MD	NY	WI
Medicaid	11%	8%	8%	16%	8%
Medicare	6%	7%	6%	7%	7%
No Charge	0%	3%	1%	0%	0%
Other	4%	4%	1%	2%	2%
Private Insurance	77%	74%	79%	71%	80%
Self-Pay	3%	4%	4%	4%	3%
Total	100%	100%	100%	100%	100%

Table A-18 looks at variation in inpatient and ambulatory setting of care by payer and procedure.

Table A-18 Variation in setting of care by procedure and payer

Payer/Setting of Care	Total	Myomectomy	Abdominal Hysterectomy	Laparoscopic Hysterectomy	Vaginal Hysterectomy	Uterine Artery Emb.	Blood Transfusion
Medicaid							
Ambulatory	15%	18%	0%	18%	6%	10%	1%
Inpatient	85%	82%	100%	82%	94%	90%	99%
Medicare							
Ambulatory	27%	63%	0%	28%	5%	11%	1%
Inpatient	73%	37%	100%	72%	95%	89%	99%
No Charge							
Ambulatory	25%	21%	7%	13%	5%	54%	3%
Inpatient	75%	79%	93%	87%	95%	46%	97%
Other							
Ambulatory	23%	25%	0%	27%	7%	39%	3%
Inpatient	77%	75%	100%	73%	93%	61%	97%
Private Insurance							
Ambulatory	33%	35%	1%	37%	13%	32%	3%
Inpatient	67%	65%	99%	63%	87%	68%	97%
Self-Pay							
Ambulatory	22%	33%	1%	38%	4%	9%	3%
Inpatient	78%	67%	99%	62%	96%	91%	97%

The contrast between Medicaid and private payer is again evident. In total, 85 percent of procedures are inpatient for Medicaid-covered patients, as opposed to 67 percent for patients covered by private insurance. Looking specifically at the Medicaid-to-private-insurance

comparison, not only are Medicaid uterine fibroid patients hospitalized more they also experience longer stays on average, as depicted in Table A-19.

Table A-19 Length of stay for inpatient uterine fibroid care in Medicaid and private insurance

Values	Medicaid	Private Insurance
Inpatient-Only Statistic		
Mean length of inpatient stay	3.5	2.9
Median length of inpatient stay	3.0	3.0
Std dev length of inpatient stay	3.0	1.8

Medicaid Longitudinal Overview

The national Medicaid Analytic Extract (MAX) contains all claims and enrollment data for more than 40 million Medicaid beneficiaries. The data are extremely detailed and provide complete treatment histories during periods of program enrollment. The data are complete for Medicaid beneficiaries who are financed by the State on a fee-for-service (FFS) basis.[a] The claims data include treatments by all provider types. Each claim has an individual patient identifier on it and includes diagnosis and procedure data. The MAX source permits longitudinal analyses of patient care pathways across provider and across time.

The analysis of how uterine fibroids patients are diagnosed and treated over time is well supported by administrative data records with unredacted patient identifiers. There are several major limitations. As can be observed in the statistics presented above, only approximately 12 percent of uterine fibroid patients who receive care in a hospital or clinic setting are Medicaid-enrolled. The degree to which the experience of Medicaid beneficiaries can be generalized to other populations is unknown. The Medicaid population is younger, has a smaller proportion of white patients, and experiences shorter lengths of stay when hospitalized. The impact of the demographic differences and differences in payment rates between a Medicaid population and privately insured population may be substantial. An additional problem is the transient nature of Medicaid eligibility. Medicaid beneficiaries eligible due to pregnancy or dependent children may be restricted in their episode of program enrollment. Medicaid beneficiaries eligible due to disability may have continuous eligibility in the study period but may be concurrently eligible for Medicare. The Medicaid-Medicare dual eligibles are not included in the Medicaid analyses since only limited information is available on medical services from Medicaid program data.

In order to perform longitudinal analyses from case identification through a clinical endpoint a substantial amount of enrolled history must be available. To identify an incident case of uterine fibroid disease, at least 12 months of continuous enrollment with no prior diagnosis is required. In order to fully analyze care, clinical pathways, and outcomes, years of post-index identification data may be required.

MAX claims and enrollment data from 2001–2005 were used to identify uterine fibroid cases and to prepare longitudinal analyses of care sequences. Cases were identified from

[a]Non-FFS beneficiaries enrolled in managed care will be present in the enrollment data but may have incomplete utilization histories since there is no history of claims being submitted by providers for payment to the State Medicaid Management Information System. Instead, capitation payments are made by the program to managed care plans, who then pay the providers. The collection of service-level information from managed care plans and its storage in the MAX database is very incomplete.

physician and hospital claims. Cases were indexed to first reported diagnosis. Incident cases were identified based on the presence of at least 12 months of Medicaid enrollment prior to first diagnosis and at least 12 months of followup eligibility.

Annual analyses were prepared for all uterine fibroid patients starting with the first year a diagnosis was observed. For patients with at least 6 months of fee-for-service eligibility in the year annual treatment profiles were generated. The annual profiles of all cases with a diagnosis within the year were used for cross-sectional analyses. A second study group consisted of incident cases. For this population, treatment summaries were prepared for each fee-for-service 12 month increment from the index date. The incident population was followed until the loss of eligibility or the end of the database in 2005.

For both study groups the underlying data were organized as person-level, longitudinal records with monthly markers for uterine fibroid–related diagnoses and treatments. The annual summary statistics are built from the monthly markers of diagnoses, procedures, drug codes, and other related health care services.

Medicaid CY 2005: Cross-Site of Care Profiles by Treatment Type

The strength of the Medicaid data is its capacity to support the analysis of care across provider and over time. The CY 2005 tabulation of treatments and complications in Table A-20 is also stratified by major procedure type. Each column presents rates of cotreatments and complications as a function of major procedure type.

Table A-20. National Medicaid profile of treatment and complication rates in CY 2005 by surgery type

CY 2005 Measure	All UF Patients	Abdominal Hysterectomy	Laparoscopic Hysterectomy	Myomectomy	Vaginal Hysterectomy	Excision/ Destruction Lesion of Uterus	Uterine Artery Embolization	No Major Procedure
UF Patients	44,549 (100%)	6,612 (15%)	1,321 (3%)	661 (1%)	1,541 (3%)	247 (1%)	350 (1%)	33,562 (75%)
Treatments								
Abdominal hysterectomy	15%	100%	4%	7%	3%	6%	14%	0%
Removal of tubes and ovaries	11%	52%	49%	8%	29%	7%	12%	0%
Laparoscopic hysterectomy	3%	1%	100%	3%	3%	1%	1%	0%
Vaginal hysterectomy	3%	1%	3%	1%	100%	1%	2%	0%
Excision/destruction lesion of uterus	1%	0%	0%	1%	0%	100%	1%	0%
Uterine artery embolization	1%	1%	0%	2%	0%	1%	100%	0%
Myomectomy	1%	1%	2%	100%	0%	4%	3%	0%
Blood transfusion	4%	10%	4%	12%	4%	6%	14%	3%
Complications								
Medical/surgical complication	10%	28%	17%	18%	16%	13%	20%	6%
Urinary tract infection	20%	24%	24%	16%	23%	19%	29%	19%
Fever/pyrexia	5%	8%	7%	7%	6%	4%	14%	4%
Wound infection	1%	2%	2%	2%	2%	2%	1%	1%
Venous thrombosis/embolus	1%	1%	1%	0%	1%	0%	2%	0%
Menopausal symptoms	5%	9%	9%	1%	7%	6%	4%	4%
Rxs								
GnRH agonists	2%	2%	3%	5%	1%	1%	3%	2%
Medroxyprogesterone acetate—oral	7%	7%	5%	7%	7%	6%	3%	7%
Medroxyprogesterone acetate—depot	2%	1%	1%	2%	1%	2%	2%	2%
Oral contraceptives	22%	14%	15%	28%	17%	22%	17%	25%
NSAID	52%	64%	69%	61%	65%	43%	59%	48%

The table demonstrates differences in complication rates as a function of treatment. As noted in the analysis of the SID and SASD five-State data source, hysterectomy type varies considerably between States. As can be seen in the table above, there are differences in complication rates, with abdominal hysterectomies leading to the highest rates of surgical complications.

Medicaid CY 2002 Initiation Cohort: Clinical Pathways by Treatment Type

The Medicaid data were also used to look at multiyear patterns of care by major surgery type. A cohort of CY 2002–incident uterine fibroid patients who stayed in Medicaid through the end of CY 2005 were studied for multiyear patterns and sequences of care. Table A-21 below profiles in 12-month segments (Y1–Y4), anchored to a patient-index date, the rates of treatment and complications in the followup years. The subtables are organized by the major surgery type observed in the first 12 months post index date. The tables are further stratified in Tables A-22, A-23, and A-24, respectively, by reports of rates of treatments, complications, and related drug therapies. It should be noted that, given the end of the database in December 2005, not all incident cases will have a full four years of followup. If incidence is evenly distributed across CY 2002, then only half of the fourth followup year will be available.

Table A-21. Rates of treatment for uterine fibroids and complications in followup years

	Year 1 All Procedures	YR 1 Abdominal Hysterectomy	YR 1 Laparoscopic Hysterectomy	YR 1 Myomectomy	YR 1 Vaginal Hysterectomy	YR 1 Other Procedure
CY 2002 Incident Cohort	18,625	3,016 (16%)	410 (2%)	194 (1%)	806 (4%)	13,885 (75%)
Abdominal hysterectomy						
YR 1	16%	100%	5%	16%	5%	0%
YR2	2%	0%	0%	2%	0%	3%
YR3	2%	0%	0%	3%	0%	2%
YR4	1%	0%	0%	1%	0%	1%
Laparoscopic hysterectomy						
YR 1	2%	1%	100%	3%	5%	0%
YR2	0%	0%	0%	2%	0%	0%
YR3	0%	0%	0%	1%	0%	0%
YR4	0%	0%	0%	0%	0%	0%
Vaginal hysterectomy						
YR 1	4%	1%	9%	1%	100%	0%
YR2	1%	0%	0%	2%	0%	1%
YR3	0%	0%	0%	1%	0%	0%
YR4	0%	0%	0%	0%	0%	0%
Removal of tubes and ovaries						
YR 1	13%	50%	36%	14%	37%	0%
YR2	4%	2%	2%	4%	2%	3%
YR3	3%	1%	1%	4%	2%	2%
YR4	2%	1%	1%	2%	1%	1%
Myomectomy						
YR 1	1%	1%	1%	100%	0%	0%
YR2	0%	0%	0%	1%	0%	0%
YR3	0%	0%	0%	1%	0%	0%
YR4	0%	0%	0%	0%	0%	0%

Table A-21. Rates of treatment for uterine fibroids and complications in followup years (continued)

	Year 1 All Procedures	YR 1 Abdominal Hysterectomy	YR 1 Laparoscopic Hysterectomy	YR 1 Myomectomy	YR 1 Vaginal Hysterectomy	YR 1 Other Procedure
Uterine artery embolization						
YR 1	1%	1%	1%	2%	1%	1%
YR2	1%	1%	1%	0%	0%	1%
YR3	1%	1%	1%	1%	0%	1%
YR4	0%	0%	0%	0%	0%	0%
Excision/destruction lesion of uterus						
YR 1	1%	1%	0%	2%	0%	1%
YR2	0%	0%	0%	1%	0%	0%
YR3	0%	0%	0%	0%	0%	0%
YR4	0%	0%	0%	0%	0%	0%
Blood transfusion						
YR 1	3%	7%	4%	8%	5%	2%
YR2	1%	1%	0%	1%	0%	1%
YR3	2%	1%	1%	2%	1%	2%
YR4	1%	1%	0%	1%	1%	1%
Complications Y1-Y4						
Medical/surgical complications						
YR 1	12%	30%	21%	19%	21%	7%
YR2	7%	10%	9%	4%	8%	7%
YR3	7%	10%	8%	6%	9%	7%
YR4	6%	7%	8%	4%	7%	5%

Table A-21. Rates of treatment for uterine fibroids and complications in followup years (continued)

	Year 1 All Procedures	YR 1 Abdominal Hysterectomy	YR 1 Laparoscopic Hysterectomy	YR 1 Myomectomy	YR 1 Vaginal Hysterectomy	YR 1 Other Procedure
Venous thrombosis/embolus						
YR 1	0%	1%	0%	1%	1%	0%
YR2	0%	0%	0%	0%	0%	0%
YR3	0%	0%	0%	0%	0%	0%
YR4	0%	0%	0%	1%	0%	0%
Menopausal symptoms						
YR 1	9%	13%	17%	6%	9%	8%
YR2	6%	10%	12%	5%	9%	5%
YR3	6%	8%	12%	5%	7%	5%
YR4	3%	4%	4%	2%	3%	3%
Wound infection						
YR 1	2%	3%	2%	2%	2%	1%
YR2	1%	1%	0%	2%	0%	1%
YR3	0%	0%	0%	3%	0%	0%
YR4	0%	0%	0%	0%	1%	0%
Urinary tract infection						
YR 1	22%	27%	27%	24%	26%	21%
YR2	20%	20%	17%	18%	20%	20%
YR3	18%	18%	15%	18%	18%	19%
YR4	11%	11%	10%	9%	10%	11%
Fever/pyrexia						
YR 1	5%	8%	6%	8%	6%	4%
YR2	5%	5%	6%	4%	4%	5%
YR3	5%	5%	7%	4%	3%	5%
YR4	3%	3%	2%	3%	2%	2%
GnRH agonists						
YR 1	2%	3%	2%	5%	1%	1%
YR2	1%	0%	0%	2%	0%	1%
YR3	1%	0%	0%	0%	0%	1%
YR4	0%	0%	0%	1%	0%	0%

Table A-21. Rates of treatment for uterine fibroids and complications in followup years (continued)

	Year 1 All Procedures	YR 1 Abdominal Hysterectomy	YR 1 Laparoscopic Hysterectomy	YR 1 Myomectomy	YR 1 Vaginal Hysterectomy	YR 1 Other Procedure
Medroxyprogesterone acetate—oral						
YR 1	9%	8%	9%	11%	11%	9%
YR2	4%	0%	0%	4%	0%	5%
YR3	3%	0%	1%	2%	0%	4%
YR4	2%	0%	0%	1%	0%	2%
Medroxyprogesterone acetate—depot						
YR 1	2%	1%	1%	1%	1%	2%
YR2	2%	0%	0%	1%	0%	2%
YR3	2%	0%	0%	1%	0%	2%
YR4	1%	0%	0%	0%	0%	1%
Oral contraceptives						
YR 1	26%	16%	19%	27%	19%	28%
YR2	15%	2%	3%	11%	2%	19%
YR3	12%	2%	3%	9%	1%	15%
YR4	7%	1%	2%	5%	0%	9%
NSAID						
YR 1	52%	62%	64%	60%	65%	48%
YR2	46%	49%	50%	45%	50%	45%
YR3	48%	51%	49%	41%	52%	47%
YR4	34%	34%	34%	25%	36%	34%

Table A-22. Uterine fibroid–related in-hospital procedure codes

Procedures	Procedure Codes Codes (P=ICD9,C=CPT/HCPC)
Myomectomy	P6829,C58140,C58145,C58146
Abdominal Hysterectomy	P684,P6849,P683,P6839,C58240,C58951,C58953,C58954,C58956, C58150- C58209
Laparoscopic Hysterectomy	P6841,P6831,P6851,C58578,C58579,C58550,C58545,C58546,C58552,C58553,C58554, C58570,C58571,C58572,C58573,C58541 -C58554
Vaginal Hysterectomy	P685,P6859 ,C58260 - C58294
Radical Hysterectomy	P686,P687,C58548,C58210
Removal of Tubes and Ovaries	P6531- P6564,C58262,C58263,C58291,C58542,C58544,C58552,C58554
Uterine Artery Embolization	P388,P3979,P9929,C37210,C58262,C58263,C58291,C58542,C58544,C58552,C58554
Excision/Destruction Lesion Of Uterus	P682',’P691',’C57500'
Focused Ultrasound	C0071T,C0072T

Table A-23. Complication of uterine fibroid surgery flagged codes

Complications	Codes (P=ICD9 Procedure, D=ICD9-CM Diagnosis, R=UB92 Revenue Center Code, C=CPT/HCPC Procedure)
Blood Transfusion	P99.02,P99.04,C36430,R0391
Accidental cut, puncture, perforation or hemorrhage during medical care	DE870
Surgical procedure as cause of abnormal reaction in patient	DE878
Medical/surgical Complications	D996.xx -D999.xx
Venous Thrombosis/embolus	D453.4,DV1251
Menopausal symptoms	D627.2
Gastritis	D535.4
Dermatitis	D693.xx
Nephropathy	D583.9
Wound Infection	D614.3,D614.4,D616.1,D998.5
Urinary Tract Infection	D599.0
Fever/Pyrexia	D780.6

Table A-24. Drug

GnRH Agonists	Medroxyprogesterone acetate—oral	Medroxyprogesterone acetate—depot	Oral Contraceptives	NSAID

Appendix B. Technical Working Group Members

Name	Title	Affiliation
Kelly Butterworth	Outreach Manager, Americans for Quality Health Care Project	National Partnership for Women and Families
William Catherino, M.D., Ph.D.	Associate Professor, Department of Obstetrics and Gynecology Chair of the Fibroid Special Interest Group	Uniformed Services University of the Health Sciences American Society for Reproductive Medicine
Katherine Hartmann, M.D., Ph.D.	Vice Chair for Research and Associate Professor, Department of Obstetrics and Gynecology Director	Vanderbilt University Vanderbilt AHRQ Evidence-Based Practice Center
Richard Justman, M.D.	National Medical Director, Division of Health Services	United Healthcare
Evan Myers, M.D., M.P.H.	Professor, Department of Obstetrics and Gynecology Director, Obstetrics/Gynecology Research	Duke University School of Medicine Duke Clinical Research Institute
Wanda Nicholson, M.D., M.P.H.	Professor, Department of Obstetrics and Gynecology	University of North Carolina School of Medicine
Joy Polefrone, Ph.D.	Executive Director	Fibroid Relief
James Segars, M.D.	Head, Unit of Reproductive Endocrinology and Infertility	Eunice Kennedy Shriver National Institute of Child Health and Human Development
James Spies, M.D.	Chairmen and Professor, Department of Radiology	Georgetown University
Elizabeth Stewart, M.D.	Professor, Department of Obstetrics and Gynecology	Mayo Clinic College of Medicine

Appendix C. Stakeholder Committee Members

Name	Title	Affiliation
Shilpa Amin, M.D., M.Bsc.	Medical Officer/ Uterine Fibroid Patient	AHRQ
Kelly Butterworth	Outreach Manager, Americans for Quality Health Care Project	National Partnership for Women and Families
Thomas Byrne	Director, Health Economics & Reimbursement	Boston Scientific
Amanda Calhoun, M.D., M.P.H.	Assistant Director of Women's Health	Kaiser Permanente
William Catherino, M.D., Ph.D.	Associate Professor, Department of Obstetrics and Gynecology Chair of the Fibroid Special Interest Group	Uniformed Services University of the Health Sciences American Society for Reproductive Medicine
Kristof Chwalisz, M.D., Ph.D.	Therapeutic Area Head	Abbott
Ponjola Coney, M.D.	Senior Associate Dean for Faculty Affairs	Virginia Commonwealth University
Carla Dionne	Founder and Executive Director	National Uterine Fibroids Foundation
Lynn Golumbic, M.B.A.	Vice President of Marketing and Reimbursement	InSightec, Ltd
Paula Gwynn Grant	Uterine Fibroid Patient	Director of Marketing for Mercy Housing
Katherine Hartmann, M.D., Ph.D.	Vice Chair for Research and Associate Professor, Department of Obstetrics and Gynecology Director	Vanderbilt University Vanderbilt AHRQ Evidence-Based Practice Center
Laura Hessburg	Senior Health Policy Advisor, Reproductive Health Programs	National Partnership for Women and Families
Richard Justman, M.D.	National Medical Director, Division of Health Services	UnitedHealthcare
David Lee, Ph.D.	Chief, Health Economics	General Electric Healthcare
Richard Legro, M.D.	Professor of Obstetrics and Gynecology	Penn State University College of Medicine
Ramy Mahmoud, M.D., M.P.H., FACP	Chief Medical Officer and Worldwide Vice President	Evidence-Based Medicine, ETHICON, Inc.
Sue Marone	Uterine Fibroid Patient	Immigration and Customs Enforcement Agency, DHS
Evan Myers, M.D., M.P.H.	Professor, Department of Obstetrics and Gynecology Director, Obstetrics/Gynecology Research	Duke University School of Medicine Duke Clinical Research Institute
Joan Nagel, M.D., M.P.H.	Program Director, Office of Research on Women's Health	National Institutes of Health (NIH)
Richard Nahin, M.D.	Acting Director, Division of Extramural Research Senior Advisor for Scientific Coordination and Outreach	National Center for Complementary and Alternative Medicine (NICCAM)
Retha Newbold, M.S., C.T.	Reproductive and Developmental Discipline Leader, Staff Scientist	National Institute of Environmental Health Sciences, NIH
Wanda Nicholson, M.D., M.P.H.	Professor, Department of Obstetrics and Gynecology	University of North Carolina School of Medicine
Estella Parrott, M.D., M.P.H.	Program Director of the Reproductive Medicine Gynecology Program	Eunice Kennedy Shriver National Institute of Child Health and Human Development
Joy Polefrone, Ph.D.	Executive Director	Fibroid Relief

Name	Title	Affiliation
Alan Rosenberg, M.D.	Vice President of Medical Technology Policy, Assessment and Credentialing Programs	WellPoint, Inc.
John Santa, M.D.	Medical Director	Consumer Reports Health Ratings Center
James Segars, M.D.	Head, Unit of Reproductive Endocrinology and Infertility	Eunice Kennedy Shriver National Institute of Child Health and Human Development
Howard Sharp, M.D.	Associate Professor	University of Utah School of Medicine American College of Obstetrics and Gynecology
Jean Slutsky, M.S.P.H.	Director, Effective Healthcare Program	Center for Outcomes and Evidence, AHRQ
Scott Smith, Ph.D.	Director, DEcIDE Effective Healthcare Program	AHRQ
James Spies, M.D.	Chairman and Professor, Department of Radiology	Georgetown University
Brian Stainken, M.D.	Professor and Chairman, Diagnostic Imaging President	Roger Williams Medical Center Society for Interventional Radiology
Elizabeth Stewart, M.D.	Professor, Department of Obstetrics and Gynecology	Mayo Clinic College of Medicine
Sara Strickler, M.D.	Medical Director	MED Institute, Cook, Inc.
Kathleen Uhl, M.D.	Assistant Commissioner for Women's Health; Director	Office of Women's Health, FDA
Meera Viswanathan, Ph.D.	Health Services Researcher	RTI
Robert Vowels, M.D., M.P.H.	Medical Director	District of Columbia Department of Health Care Finance (DHCF)
Nancy Walczak, Ph.D., FSA, MAAA	Managing Director for Actuarial Consulting	Ingenix Consulting
Allan Warshowsky, M.D., PC	Private Physician (Ob-Gyn)	Founding Diplomat of American Board of Integrative Medicine
Maura Whiteman, Ph.D.	Epidemiologist	Division of Reproductive Health, CDC

Appendix D. Initial List of Research Questions

General Evidence Gaps/Epidemiology

- What are the incidence, prevalence, and burden of disease of symptomatic uterine fibroids in the United States? (AHRQ 2007)
- What are the incidence and prevalence of asymptomatic uterine fibroids in the United States? (AHRQ 2001)
- What are the epidemiological, social (e.g., chronic stress and lifestyle factors) and other socioeconomic factors (including those that might explain observed differences in the occurrence of fibroids) among women of different ethnic groups with uterine fibroids? (AHRQ 2001)
- What is the contribution of environmental exposures (e.g., environmental estrogens) to fibroid development, growth, and symptomatology?
- What is the contribution of inflammation to fibroid development, growth, and symptomatology?
- What is the contribution of nutrition (both over- and under-intake of specific dietary components) to fibroid growth, development, and symptomatology?
- What is the natural history of uterine fibroids, in terms of fibroid growth and symptomatology, among women who choose watchful waiting? (AHRQ 2007)
- What are the risks and benefits of expectant management for symptomless women with uterine fibroids? (AHRQ 2007)
- How do factors such as age, race/ethnicity, smoking status, history of pregnancy, history of births, history of contraceptive use, body mass, and menopausal status affect the natural history of disease?
- Are there genotypes, gene mutations, or epigenetic modifications that differ by race or ethnic group, that may account for differences in the incidence and natural history (including rate of growth and symptom patterns) of disease among these groups? (AHRQ 2001)
- What individual interventions (e.g., watchful waiting, monotherapy or polytherapy medical therapy, myomectomy, hysterectomy, or nonsurgical invasive) and/or combinations are most frequently used as primary treatment in outpatient and inpatient uterine fibroid management, and how does this vary by patient characteristic (e.g., by childbearing aims, age, race, fibroid subtypes, insurance type), provider characteristic, and geography?
- What percentages of women have had their uterine fibroid symptoms spontaneously resolve, and what is the average duration of symptomatic uterine fibroids for these women?
- What genetic biomarkers or environmental, nutritional, socioeconomic, or other factors (in addition to onset of menopause) affect the likelihood of spontaneous symptom resolution?

Comparative Cost Data

- What is the relative cost-effectiveness of the various medical treatments (including GnRH agonists, NSAIDS, synthetic steroids [mifepristone or RU486], estrogen receptor

modulators, progestins, aromatase inhibitors, antifibrinolytics, and/or oral or intrauterine contraceptives) for uterine fibroids?
- What is the relative cost-effectiveness of the surgical treatments (including but not limited to total abdominal and vaginal hysterectomy, hysteroscopy, UAE, MRgFUS, endometrial ablation, and myomectomy) for uterine fibroids?
- What is the relative cost-effectiveness of lifestyle change versus surgical or medical interventions for fibroid symptom relief?

Diagnosis and Education

- Which common classifications (i.e., staging, standard methods for assessing and reporting baseline symptoms, uterine anatomy, and responses to treatment) should be used in research about women who present with uterine fibroids? (AHRQ 2001, AHRQ 2007)
- How can researchers best define nomenclature and descriptive details, such as inclusion/exclusion parameters, fibroid type, and position in the uterus, that are likely to guide selection of treatments or affect treatment outcomes? (AHRQ 2007)
- What educational and behavioral modalities are effective in supporting and helping women manage clinically significant uterine fibroids? (RFTO)
- How can researchers understand and overcome historical barriers to minority participation in research for this disease that adversely affects African-American women?

Evidence Gaps Pertinent to the Management of Uterine Fibroids in Women Who Wish to Bear Children in the Future

Choice and Timing of Therapies

- What factors affect patient choice of treatment for the management of uterine fibroids for women who wish to bear children in the future?
- Among women who wish to bear children in the future, how does the usage of select therapies as primary versus secondary management for uterine fibroids vary by patient characteristics, geography, and provider characteristic? How does this variation affect patient health outcomes? (RFTO)

Medical Treatments

- Which of the medical therapies (including GnRH agonists, NSAIDS, anti-inflammatories, antiangiogenesis factors, synthetic steroids [mifepristone or RU486], estrogen receptor modulators, progestins, aromatase inhibitors, and antifibrinolytics) have negative effects on the ability to bear children in the future? (Hirst 2008)
- Do the risks and benefits in terms of future ability to bear children, for the available medical therapies (including GnRH agonists, NSAIDS, anti-inflammatories, antiangiogenesis factors, synthetic steroids [mifepristone or RU486], estrogen receptor modulators, progestins, aromatase inhibitors, and antifibrinolytics) differ by race, ethnicity, age, or other demographic characteristics?

Surgical Treatments

- What is the relative effectiveness and safety of available surgical therapies (including but not limited to hysteroscopy, UAE, MRgFUS, endometrial ablation, and myomectomy) in terms of rates of future pregnancies, percentage of failed pregnancies, cesarean section rates, adverse events, types of delivery, term of delivery, and birth weight? (RFTO, Goodwin 2008)
- Are there differences in the relative effectiveness and safety of available surgical therapies (including but not limited to hysteroscopy, UAE, MRgFUS, endometrial ablation, and myomectomy) across subpopulations (e.g., race, age, symptoms, types of fibroids, size of fibroids, radiological characteristics of fibroids) in terms of rates of future pregnancies, percentage of failed pregnancies, cesarean section rates, adverse events, types of delivery, term of delivery, and birth weight?
- What is the relative effectiveness of endometrial ablation as an additive technology rather than a substitute for hysterectomy?
- Does uterine artery embolization precipitate amenorrhea (absence of menstrual bleeding), and does this occur at an endometrial or ovarian level? (Goodwin 2008)
- What is the best method for achieving effective embolization for those who desire to become pregnant in the future?

Across Treatments

- What are the most effective strategies for outpatient care coordination for women with uterine fibroids (encompassing multiple treatments, rehabilitation, and preconceptual counseling)?
- Are there differences in the need for additional treatment after medical treatment, myomectomy, UAE, or other uterus-sparing interventions, in how long on average the intervention has beneficial outcomes before additional intervention(s) for treatment are needed? (RFTO)
- Which management strategies (individual therapies or combination of therapies) are most effective for women who wish to bear children in the future?
- What is the relative effectiveness of uterine artery embolization versus medical treatments for managing symptomatic fibroids, among women who wish to bear children? (Gupta 2006)
- Can lifestyle changes (including but not limited to dietary intake, physical activity, smoking, hormonal exposure) affect growth and development of fibroids?
- Are there differences among the interventions regarding how long fertility is impaired post-treatment? (RFTO)
- What is the relative effectiveness of complementary and alternative treatments (including but not limited to acupuncture, herbal preparations, nutritional supplements, and changes in diet) versus traditional interventions for uterine fibroids among women who wish to bear children? (AHRQ 2007, Liu 2009)

Evidence Gaps Pertinent to the Management of Uterine Fibroids in Women Who Do Not Wish to Bear Children in the Future

Choice and Timing of Therapies

- What factors affect patient choice of treatment for the management of uterine fibroids for women who do not wish to bear children in the future?
- Among women who do not wish to bear children in the future, how does the usage of select therapies as primary versus secondary management for uterine fibroids vary by patient characteristics, geography, and provider characteristics? How does this variation affect patient health outcomes? (RFTO)

Medical Treatments (Generic Across Childbearing Aim)

- What is the relative effectiveness (e.g., on slowing or stopping fibroid growth, durability of symptom relief, percentage of fibroids recurring) and safety of available medical therapies (including GnRH agonists, NSAIDS, anti-inflammatories, antiangiogenesis factors, synthetic steroids [mifepristone or RU486)] estrogen receptor modulators, progestins, aromatase inhibitors, antifibrinolytics, and/or oral or intrauterine contraceptives)? (AHRQ 2007, Liu 2009, RFTO)
- Are there differences across subpopulations (e.g., race, age, symptoms, types of fibroids, size of fibroids, radiological characteristics of fibroids) in the relative effectiveness (e.g., on slowing or stopping fibroid growth, durability of symptom relief, percentage of fibroids recurring,) and safety of available medical therapies (including GnRH agonists, NSAIDS, anti-inflammatories, antiangiogenesis factors, synthetic steroids [mifepristone or RU486], estrogen receptor modulators, progestins, aromatase inhibitors, antifibrinolytics, and/or oral or intrauterine contraceptives)?
- What are the effects on the aging process of medical therapy for treatment of clinically significant uterine fibroids?

Surgical Treatments (Generic Across Childbearing Aim)

- What is the relative effectiveness (e.g., on slowing or stopping fibroid growth, durability of symptom relief, percentage of fibroids recurring, bleeding symptoms, percentage requiring further surgery), and safety of available surgical therapies (including but not limited to total abdominal and vaginal hysterectomy, hysteroscopy, UAE, MRgFUS, endometrial ablation, and myomectomy)? (RFTO)
- Are there differences across subpopulations (e.g., race, age, symptoms, types of fibroids, size of fibroids, radiological characteristics of fibroids) in relative effectiveness (e.g., on slowing or stopping fibroid growth, durability of symptom relief, percentage of fibroids recurring, percentage requiring further surgery) and safety of available surgical therapies (including but not limited to total abdominal and vaginal hysterectomy, hysteroscopy, UAE, MRgFUS, endometrial ablation, and myomectomy)?
- What are the risks and benefits (others than those surrounding fertility) of hysterectomy and myomectomy in the treatment of symptomatic and asymptomatic fibroids? (AHRQ 2001)

- What are the risks associated with single versus multiple myomectomies? (i.e., Do women with a solitary clinically apparent fibroid have different outcomes after surgical management than women with multiple fibroids?) (AHRQ 2001)
- What is the best method for achieving effective embolization? (Hirst 2008)
- What is the effect of prophylactic antibiotics in preventing complications and side effects associated with uterine artery embolization? (Hirst 2008)
- What are the effects of surgical management of uterine fibroids, especially hysterectomy, on the aging process? (AHRQ 2001)

Across Treatments

- What is the relative effectiveness of UAE versus medical or surgical treatments for managing symptomatic fibroids? (Gupta, 2006)
- What is the effectiveness of complementary and alternative treatments (including, but not limited to acupuncture, herbal preparations, nutritional supplements, and changes in diet) versus traditional interventions for uterine fibroids? (AHRQ 2007, Liu 2009)
- What are the differences among interventions in short- and long-term outcomes including physical limitations and emotional stressors and/or psychological symptoms and diagnoses? (RFTO)

Menopause

- In menopausal women, do hormone replacement regimens interfere with fibroid resolution?
- Is hormone replacement therapy associated with higher rates of recurrent fibroids after uterine artery embolization? (Hirst 2008)

Outcomes Measurement

- What are the best validated instruments for measuring patient reported outcomes following treatment for uterine fibroids? (AHRQ 2007, Harding 2008)
- Are there validated time-to-event instruments for measuring outcomes following treatment for uterine fibroids? (AHRQ 2007)

References Used in Identification of Research Questions

Cochrane Database of Systematic Reviews

Lui JP, Yang H, Xia Y, et al. Herbal preparations for uterine fibroids. Cochrane Database Syst Rev 2009 Apr;15(2):CD005292

Ke LQ, Yang K, Li J, et al. Danazol for uterine fibroids. Cochrane Database Syst Rev 2009 Jul;8(3):CD007692

Gupta JK, Sinha A, Lumsden MA, et al. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev 2006;1:CD005073. DOI:10.1002/14651858.

Other Reviews/Articles

Myers ER, McCrory DC, Barber MA, et al. Management of Uterine Fibroids. Evidence Report/Technology Assessment No. 34 (Prepared by Duke University under Contract No. 290-97-0014). Rockville, MD: Agency for Healthcare Research and Quality. July 2001.

Evidence Report/Technology Assessment No. 154. Management of Uterine Fibroids: An Update of the Evidence. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016). Rockville, MD: Agency for Healthcare Research and Quality. AHRQ Publication No. 07-E011. July 2007

Carls GS, Lee DW, Ozminkowski RJ, et al. What are the total costs of surgical treatment for uterine fibroids? J Women's Health 2008;17(7):1119-1132

Hirst A, Dutton S, Wu O, et al. A multi-centre retrospective cohort study comparing the efficacy, safety and cost effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study. Health Technol Assess 2008;12(5):1-248.

Goodwin SC, Spies J, Worthington-Kirsch R, et al. The FIBROID Registry: long-term outcomes. Obstet Gynecol 2008;111:22-33

Spies JB, Runback JH, Ascher S, et al, SIR Foundation. Development of research agenda for uterine artery embolization: proceeding from a multidisciplinary research consensus panel. J Vasc Interv Radiol 2006;17:1871-1879.

O'Sullivan, Thompson D, Chu P. Cost-effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids. International J of Tech Assessment In Health Care 2009;25:14-25.

Bradley LD. Uterine fibroid embolization: a viable alternative to hysterectomy. Am J Obstet Gynecol 2009 Aug;201(2):127-135.

Harding G, Coyne KS, Thompson CL, et al. The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). Health Qual Life Outcomes 2008 Nov 12;6:99.

Appendix E. Results of TWG Rescoring of Research Questions

Rank	Question	Mean	Min	Max	Avg. Deviation
1	Q12: (Relative effectiveness) What is the relative effectiveness of interventions (medical or surgical) for treating uterine fibroids?	9.625	9	10	0.469
2	Q3. (Methods) What are the characteristics of validated and reliable classification systems of patient reported outcomes (including patient preferences, disease-specific and general quality of life, and patient satisfaction) to use in research and clinical care of women with uterine fibroids?	8.875	7	10	0.688
3	Q2. (Methods) What are the characteristics of validated and reliable classification systems of standard anatomic staging to use in research and clinical care of women with uterine fibroids?	8.714	7	10	0.980
4	Q5. (Natural History) What is the incidence, prevalence, and burden of disease (accounting for misclassification of symptoms) of fibroids in the United States?	8.000	7	10	0.500
5	Q6. (Natural History) What is the natural history of uterine fibroids in terms of fibroid growth, regression, and symptomatology among women who choose watchful waiting over durations longer than 6 months? What factors including age, race/ethnicity, smoking status, reproductive history, history of contraceptive use, body mass, family history, and menopausal status affect the natural history of disease?	8.000	6	10	0.750
6	Q10. (Care Coordination and Shared Decisionmaking) What are the most effective dissemination approaches for providing patients and providers with the best evidence on fibroid management, and do these vary across different subpopulations?	7.875	6	10	1.125
7	Q8. (Care Coordination and Shared Decisionmaking) How do patients and providers currently identify and choose strategies for fibroid management (including acquisition and processing of available information and patient-provider communication)?	7.625	5	10	1.313
8	Q7. (Genetics) Are there genotypes, gene mutations, gene/environment interactions, epigenetic modifications, or other biomarkers that differ by race or ethnic group that may account for differences in the incidence, natural history, and treatment response (including rate of growth and symptom patterns) of disease among these groups?	7.625	4	10	1.719
9	Q1. (Patterns of Use) What individual strategies (e.g., watchful waiting, lifestyle changes), or combinations (including different sequencing) of strategies are most frequently used as treatment in fibroid management? How does this vary by patient characteristics (childbearing aim, age, language, demographics, insurance status, provider characteristics, patient preference, social/cultural factors and geography)?	7.500	5	10	1.375
10	Q9. (Care Coordination and Shared Decisionmaking) How do different strategies for shared decisionmaking affect outcomes, especially patient-reported outcomes?	7.500	4	10	1.500
11	Q4. (Methods) What are the characteristics of validated and reliable classification systems of measures of responses to specific symptoms (such as menstrual pictograms, menstrual diaries, hemoglobin) to use in research and clinical care of women with uterine fibroids?	7.500	3	10	1.500

Rank	Question	Mean	Min	Max	Avg. Deviation
12	Q11. (Care Coordination and Shared Decisionmaking) What methods of coordinating care among different providers are most effective in improving outcomes?	6.625	1	10	2.219

Appendix F. Glossary of Terms

Alkaline hematin method. Standard technique for measuring menstrual blood loss. Hemoglobin levels are determined from collected sanitary items from a single cycle to give an estimate of blood loss.

Hysterectomy. A surgical procedure to remove the uterus. There are two basic types of hysterectomies: total, which is the complete removal of the uterus; and subtotal, which leaves the uterine cervix intact. Several surgical approaches to removing the uterus exist, including abdominal hysterectomy, laparoscopically assisted hysterectomy, laparoscopic hysterectomy, and vaginal hysterectomy.

Myomectomy. A surgical procedure to remove the uterine fibroids and repair of the defect in the uterine wall, without the complete removal of the uterus. There are a number of different surgical approaches to removing uterine fibroids that leave the uterus intact, including abdominal myomectomy, laparoscopically assisted myomectomy, laproscopic myomectomy, and hysteroscopic myomectomy.

Uterine artery embolization (UAE). A minimally invasive procedure where small particles are injected via a catheter into the arteries that supply blood to the fibroid. Cutting off the blood supply will cause the fibroid to shrink and soften.

Magnetic resonance image-guided focused ultrasound. A procedure where an MRI thermal imaging system is used to locate and then guide sound waves from an ultrasound directly to the fibroid. The sound waves produce energy to raise the temperature of the tissue, thereby destroying the fibroid while only minimally affecting the surrounding tissue. The destruction of the fibroid is monitored with the MRI thermal imaging system.

Menstrual diaries. Technique for measuring menstrual bleeding. During each cycle, the patient records how many tampons are needed each day and the number of days of bleeding per cycle.

Menstrual pictogram. Technique for measuring menstrual bleeding. A pictorial blood loss assessment chart (PBAC), which is a visual representation of menstrual blood loss, is used. The chart consists of a series of diagrams representing lightly, moderately, and heavily soiled tampons or towels. A numerical scoring system coincides with the amount of blood lost.