An Agenda for Research into Uterine Artery Embolization: Results of an Expert Panel Conference[1]

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Abbreviations: RCT = randomized controlled trial, UAE = uterine artery embolization

PURPOSE: To develop a research agenda for uterine artery embolization (UAE) for the treatment of symptomatic leiomyomata.

MATERIALS AND METHODS: An expert panel was convened to examine data and develop a consensus for UAE research. Panelists reviewed data from articles about UAE and data on hysterectomy and myomectomy, which were abstracted into evidence tables. A modified Delphi process was used to rate the importance of measuring specific outcomes and a nominal group process was used to develop ideas for study designs.

RESULTS: Panelists agreed that UAE studies would have to examine certain key measures. Outcomes identified as either "important to measure" or "essential to measure" were death, reoperation, operative injury, menorrhagia, premature menopause, recurrence of myomata, and satisfaction. The panel proposed four areas for research: randomized trial, prospective registry, disease-specific quality-of-life instrument, and cost analysis.

CONCLUSIONS: Symptomatic uterine leiomyomata are a major health concern for women. New techniques that promise to provide symptom relief deserve careful consideration. Traditionally, surgical procedures have been poorly studied until after they have been widely used. If the process described in this article can guide the acquisition of knowledge in this field, it may serve as a model for evaluating other new technologies before they become widely adopted.

UTERINE artery embolization (UAE) is an emerging minimally invasive technology for reducing symptoms of uterine fibroids. It has been proposed as a less invasive alternative to current treatment for these common, benign uterine tumors (1). Gynecologists in the United States perform more than 150,000 hysterectomies and 35,000 myomectomies each year to relieve symptoms of uterine fibroids (2,3). Therefore, if research demonstrates its safety and efficacy, UAE has the potential to benefit hundreds of thousands of patients each year. Despite this large potential benefit, the current body of research on UAE is quite limited, with 800 procedures reported in the literature and no trials prospectively comparing UAE to more conventional procedures. This study used an expert panel approach to develop an agenda for research into this new technique.

METHODS

A 10-member expert panel was convened at our institution to examine and develop a consensus for research in the field of UAE. Panel members were chosen to provide breadth of knowledge and represented diverse interests. They were identified through medical specialty

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societies and by staff at our institution. Panelists included interventional and noninterventional radiologists, obstetrician-gynecologists, a medical ethicist, experts on technology assessment and health policy, and a consumer advocate. Economists, health services researchers, and a statistician also attended the meeting. Expert panel members are listed in Appendix A.

Trained researchers performed a literature review of Medline from 1966 to May 1999, searching for the terms "uterine fibroid embolization," "uterine artery embolization," "leiomyomata and embolization," "fibroids and embolization," and "embolization and uterus." Data on hysterectomy were derived from a comprehensive review of the literature on hysterectomy published in 1996 and from a systematic review of evidence published since 1996. Data on myomectomy were obtained with use of a search strategy similar to the one previously outlined, substituting "uterine leiomyomata" and "myomectomy, outcomes and complications" as the search terms. Details of the literature search process have been published (3).

Data from articles about UAE and data on the two most common invasive treatments for uterine leiomyomata—hysterectomy and myomectomy—were abstracted into evidence tables, which were reviewed by the expert panel. These evidence tables have been published (3).

Before the meeting, panelists were provided with background on uterine myomata, UAE, hysterectomy, and myomectomy. They were also given the UAE evidence table, a literature summary, and the original articles used to create the evidence tables. Panelists were presented with a list, developed by staff at our institution, of 41 outcomes that could potentially be measured in studies of treatments for leiomyomata. At the meeting, panelists used a modified Delphi process to rate the importance of measuring each of these outcomes. This process, originally designed to synthesize expert opinion about the appropriateness of medical or surgical procedures in specific circumstances, has been described in detail (4). Experts reviewed a list of outcomes and rated them independently and anonymously. The outcomes with the highest group rating were discussed and several new ones were added. Participants then rated the outcomes independently a second time. The panel then discussed the feasibility and importance of collecting key outcome measures with use of a variety of experimental designs.

RESULTS

Panelists agreed that, to be accepted by clinicians, studies of UAE would have to examine certain key measures. In the final round of ratings, all 10 panelists identified a variety of short-term (defined as occurring fewer than 45 days after the procedure) and long-term outcomes as either "important to measure" or "essential to measure" in studies comparing UAE to other invasive treatment modalities. These included: death, reoperation (eg, hysterectomy for infection after UAE), operative injury, menorrhagia, premature menopause, recurrence of myomata, satisfaction, and technical failure rate of the procedure. The final outcome ratings for the panel are given in **Table 1**.

The literature review, evidence

Table 1
Final Panel Ratings: Key Outcome Measures for Studies of UAE

Outcome Measure	All Panelists Rate Important or Essential	Majority Rate Essential; None Rate "Do Not Measure"
Short-Term Outcomes (<45 days after procedure)		
Death	X	
Transfusion		X
Reoperation	X	
Operative injury	X	
Operative site infection		X
Pain		X
Long-Term Outcomes (>44 days after procedure)		
Physical Health		
Death	X	
Menorrhagia	X	
Anemia		X
Premature menopause	X	
Recurrence of fibroids requiring hysterectomy or myomectomy	X	
Mental Health		
Mental Health Index from SF-36	X	
Sexual Function		
Enjoyment of sexual activity		X
Frequency of sexual activity		X
Pain during sexual activity	X	
Satisfaction		
Satisfaction with treatment	X	
Cost		
Direct Cost		X
Indirect Cost		X
Use of services		
Length of Hospital Stay		X
Number of follow-up visits until full recovery		X
Technical failure rate	X	
Other		
Use of medical therapy after procedure	X	
QOL as rated by disease specific measure	X	

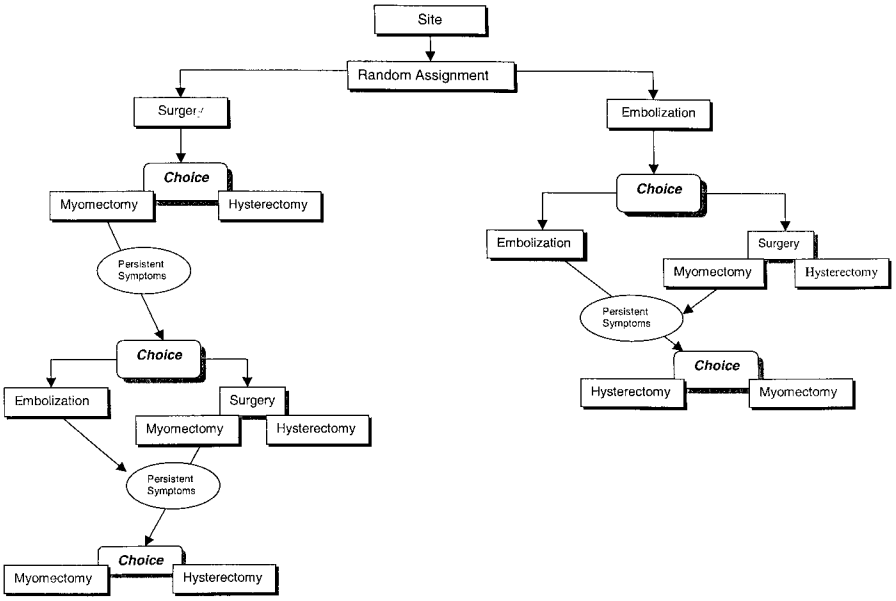

Figure 1. Randomized Control Trial Study Design.

tables, and outcome ratings were used by the panelists as a basis to discuss the direction of future uterine artery embolization research. The majority of panelists agreed that case series could not be used as the sole basis to support the general use of UAE in place of more standard treatments, and that unless there was high-quality data comparing it favorably to more widely practiced invasive treatments (ie, hysterectomy and myomectomy), UAE would not become a generally accepted treatment.

The nominal group process allows each member of the group to speak without interruption, followed by a period of group discussion of the ideas put forward by individual members. In such a process, the panelists were invited to describe what they felt would be the single best study (without consideration of cost) to examine UAE. After all the panelists had the opportunity to describe such studies, all panelists were invited to ask questions and discuss the strengths and weakness of the various approaches. Eight distinct ideas were put forth and discussed. Consensus developed around the four research elements the panelists felt would be most likely to advance the body of research on UAE while satisfying clinicians and those who make health plan coverage decisions. These proposals were (i) a randomized trial of UAE, comparing it to surgical treatment for myomata; (ii) development of a prospective registry of patients being treated with UAE; (iii) development of a disease-specific quality of life measure for women with uterine myomata; and (iv) a comparative cost analysis of UAE and myomectomy and/or hysterectomy. Further detail on each of these proposed designs was solicited from panel members and is presented later.

• Randomized Trial of UAE

Seven panelists initially proposed randomized controlled trials (RCTs) to evaluate UAE in comparison to various other treatments for uterine myomata, and all panelists agreed that, without an RCT, embolization would be unlikely to be widely accepted by gynecologists as an effective treatment for symptomatic myomata. Several areas of concern arose during discussions of possible RCTs. Some panelists were concerned that an RCT might not enroll an adequate number of patients, because women might be reluctant to enroll in a trial randomizing them to embolization versus hysterectomy. Expert panel members also debated the proper comparison group for a randomized trial, with some suggesting hysterectomy, some suggesting myomectomy, one suggesting medical therapy, and some suggesting more than one comparison group.

After a discussion of these concerns, the group agreed that a hybrid trial, involving randomization between surgical therapy (hysterectomy or myomectomy) and UAE, would satisfy these concerns. Such a trial could be conducted as a cohort study nested within an RCT as follows: patients would be randomly assigned to surgery or UAE. The patient and her gynecologist would then make the choice between hysterectomy and myomectomy, based on clinical factors or patient preference. A patient assigned to UAE whose symptoms were not relieved would be offered the choice of repeat embolization or surgery (with the specific procedure chosen by the patient and gynecologist). Patients in whom myomectomy fails (ie, those who experience persistent significant symptoms) would be offered any of the three available treatments (hysterectomy, repeat myomectomy, or embolization).

This design, shown in **Figure 1**, has advantages and disadvantages. Key advantages include elimination of bias in patient selection, good internal validity (for the comparison of surgery vs. embolization), and high face validity among clinicians. Disadvantages include high cost, long delay in obtaining results, and less external validity (as patients are more carefully selected and procedures are more carefully carried out during an RCT than in usual clinical practice). In addition, recruiting patients into randomized trials of surgical procedures may be more difficult than recruiting for studies of nonsurgical interventions.

A hybrid design such as the one being proposed addresses some of the disadvantages of RCTs but creates additional concerns. Because an element of patient choice has been maintained, patient recruit-

ment may be easier. Fewer patients are needed to compare surgery to UAE in this trial than would be needed in a three-armed study of UAE versus myomectomy versus hysterectomy. Finally, the nested cohort design allows investigators to collect additional (nonexperimentally derived) data concurrently with the randomized portion of the trial. Potential disadvantages include potential for bias in comparisons between UAE and specific surgical treatments, because patients will not be randomly assigned to one type of surgery or another. Therefore, whereas comparisons between UAE and surgery for myomata will have high internal validity, comparisons between UAE and myomectomy specifically may be more subject to bias. This bias may be controlled for during analysis if the factors determining the choice between myomectomy and hysterectomy are carefully studied.

The panelists thought that, to improve generalizability and to speed enrollment, the RCT should involve multiple sites throughout the country. They thought that data collection should encompass all the factors that the panelists unanimously agreed were key to advancing knowledge in this field. Power calculations for these outcomes are shown in **Table 2**. Panel members agreed that data should be collected for a 3- to 5-year period after enrollment to ensure collection of adequate information on premature menopause.

Table 2
Power Calculations for Randomized Trial*

Outcome	Observed Levels†	Required Sample Size (Each Group) to Detect a Difference Between Surgery (myomectomy and hysterectomy) and UAE
Death	Hysterectomy = .01% UAE = .01%	‡
Reoperation	Hysterectomy = 0.5% Myomectomy = 1% UAE = 5%	287
Operative Injury	Hysterectomy = 1% Myomectomy = 1% UAE = 0%	970
Menorrhagia (% improved)	Hysterectomy = 100% Myomectomy = 81% UAE = 90%	3313
Premature Menopause	Hysterectomy = 1% UAE = 5%	333
Recurrence Requiring Hysterectomy or Myomectomy	Hysterectomy = 0% Myomectomy = 10% UAE = 20%	219
Mental Health	0.25 SD difference between hysterectomy/myomectomy and UAE	503
Pain during sexual activity	Hysterectomy = 85% Myomectomy = 40% UAE = 40%	82
Satisfaction with Treatment	Hysterectomy = 90% Myomectomy = 87% UAE = 87%	4243
Frequency of use of Medical Therapy after Procedure	Hysterectomy = 0% Myomectomy = 15% UAE = 15%	304

* 2-sided test with alpha = 0.05. Number in each group needed to achieve 80% power, assuming 50% of surgical group undergoes hysterectomy and 50% undergoes myomectomy.
† Based on literature or expert opinion.
‡ Because of similarity of observed death rates and the rarity of the outcome, a study with 10,000 patients per arm would have 0.23 power to detect a five-fold increase in death from UAE vs. hysterectomy.

- **Registry**

Expert panel members thought that a registry of patients undergoing UAE would be a valuable research element because of its relatively low cost and the rapidity with which such a registry could begin yielding usable data. Typically, registries are disease-based and gather data on individuals with a particular condition or exposure, without regard to the treatments they receive (eg, state cancer registry, prenatal drug exposure registry). Although panelists felt that such a registry for uterine leiomyomata might be useful, they felt it would be difficult to create unless the initiative was taken by an organization with a large, stable patient base, such as a managed care organization. As an alternative, the panel agreed that a treatment-based registry would still be a key nonexperimental method of obtaining information on UAE. The panel agreed that, although a disease-based registry might not be feasible, data on control populations should be included in the registry. Two potential control groups discussed included women with uterine myomata who were untreated and those who were treated with methods other than embolization.

- **Disease-Specific Instrument Development**

One recommendation of the expert panel concerned the need to develop an instrument to measure outcomes for UAE. No standard instruments have yet been adopted for assessing women with symptom-

atic myomata, although a variety of such instruments (including modified versions of standard tools like the SF-36) have been used in studies of UAE and of more traditional treatments (1,5–7). The panel recommended that an early goal of the proposed research would be to develop or refine such an instrument that is short and easy to administer, score, and interpret for use in a variety of UAE studies.

Such an instrument would contain a generic core battery of health-related quality-of-life items supplemented with disease-specific questions for use among women with uterine myomata. The instrument would contain clinical endpoints, symptoms, and satisfaction measures. To create this instrument, it would be critical to conduct focus groups with patients themselves to determine which outcomes ultimately matter to them. Patients in the focus groups should represent women at different stages of the disease and in different stages of treatment. A qualitative analysis of comments from focus group participants would be used to identify the range of important health-related quality-of-life concerns and would help guide the item selection process.

• Comparative Cost Analysis

In the past, acceptance of UAE would have been based on safety and efficacy considerations alone. More recently, health plans and other large purchasers have begun to assess the costs and benefits of alternative treatments and base coverage decisions on the basis of these evaluations. This trend has created demand for more rigorous standards for cost measurement (8).

The proposed study focuses on the direct medical costs of UAE. Measuring medical costs is difficult. Readily available data on provider charges may not reflect resource cost. For example, charges for UAE and hysterectomy were estimated with use of Medicare fee schedule amounts. A comparison of these estimates suggest that charges for UAE may be more than twice that of abdominal hysterectomy, but panel members expressed skepticism that UAE was in reality twice as costly to perform (9).

Economic theory suggests that, in noncompetitive markets, charges reflect provider beliefs about the prices that customers are willing to pay rather than the true cost of providing treatment (10). There is reason to think that the market for UAE is currently noncompetitive because the number of suppliers is small relative to demand and entry costs are high. These considerations are probably less true of hysterectomy, as it is so widely performed; therefore, methods other than charge comparisons should be used to compare UAE and conventional treatments.

In some cases, depending on the quality of a hospital's accounting system, it may be possible to estimate costs from charges with use of reported cost-to-charge ratios (10). Even under the best of circumstances, these measures are sensitive to hospital definitions of cost categories (ie, fixed and variable costs) and make it difficult to distinguish costs associated with treatment from those "sunk" or fixed costs that would be incurred regardless of treatment.

The panel proposed a time and motion design to overcome problems of estimating costs with administrative data. Investigators would directly monitor the treatment process and apply dollar values to each of the inputs. These values come from a variety of sources: local wage rates, acquisition costs, and physician fees or wages. Because of the high cost per observation (as compared to the use of administrative data to estimate costs), this time and motion study should be conducted at two or three sites (to improve the generalizability of the results) with 10 or fewer patients at each site. The size of this study should also depend on the degree of variation in intensity of input use at different treatment sites, and it should include multiple sites.

CONCLUSIONS

Uterine leiomyomata are a common cause of significant symptoms among women, and they can be treated with a variety of medical and surgical techniques. During the last several years, UAE, an invasive radiologic technique for controlling bleeding from fibroids, has gained popularity. In the US, fewer than 50 of these procedures were performed in 1996, but more than 800 procedures were performed in 1998, and more than 4000 procedures have been performed to date (11). For this project, we performed a literature search and systematically reviewed 17 reports with interpretable patient level data on the use of UAE to treat symptomatic fibroids. The current data on UAE are based on case series without control groups, making it impossible to accurately determine the comparative risks and benefits of the procedure (12).

We convened an expert panel to identify gaps in the current body of knowledge about UAE and suggest research that might address these gaps. We selected panelists to represent those specialists who might refer patients for UAE, perform it themselves, or perform other procedures to treat uterine myomata. The panel also included a patient advocate. The modified Delphi process we employed allowed individuals to vote anonymously on the importance of a variety of potentially measurable outcomes and to reduce their disagreement on these outcomes through discussion. The use of a nominal group process to develop ideas for studies of UAE allowed all panelists to have their views heard before attempts were made to reach consensus on the best designs.

Reports of UAE in the lay press have generated considerable enthusiasm, suggesting that demand for a nonsurgical (albeit still invasive) treatment of myomata would be high (13). The prevalence of symptomatic fibroids, the apparent high demand for a new treatment, and the rough equivalence of outcomes

among UAE, hysterectomy, and myomectomy suggest that controlled trials of these treatments would be feasible, ethical, and desirable. The majority of the expert panel concluded that beginning a properly designed RCT would be crucial in establishing the comparative risks and benefits of UAE, hysterectomy, and myomectomy. With use of a modified Delphi process, the panel also identified key outcomes to be collected in such a trial.

The type of quality-of-life measure identified by the panel as one of these key outcomes does not now exist for women with uterine myomata, and general quality-of-life measures (such as the SF-36) may be less appropriate for relatively young and healthy individuals. For these reasons, the panel decided that the development of such a measure should be a key focus of UAE research, and that, when developed, this measure could be incorporated into experimental and nonexperimental studies of UAE.

In the current health care environment, in which cost considerations are often primary when evaluating new treatments, careful study of the costs of UAE should also be a priority. There are multiple ways of measuring cost, each with its advantages and disadvantages. The panel agreed that a time and motion study would provide important information about the actual resource use of embolization, as distinct from charges for the procedure, which can vary tremendously from practitioner to practitioner. Further information about cost could also be obtained as part of a randomized trial if cost measures are included as part of the data collection design.

Finally, the panel believed that establishing a registry of patients undergoing UAE could provide nonexperimental data on the risks and benefits of UAE, patient selection, technique, and diffusion of the procedure throughout the country. The utility of a registry could be increased by soliciting data on a comparison group, either women with uterine myomata who do not undergo UAE (ie, have either standard interventions or no intervention) or an "unselected" population of women in similar demographic strata. This type of registry would be less costly to implement than a randomized trial would be and would provide information more rapidly, albeit with less reliability and validity. Registry data would be useful in identifying specific questions to be answered by an RCT but would not be a substitute for such a trial.

Symptomatic uterine leiomyomata are a significant source of distress to many women and place a substantial burden on our health care system. New techniques that promise to provide relief from this condition deserve careful consideration. Traditionally, surgical procedures have been poorly studied until after they have been widely used. The approach taken in reviewing UAE involved a careful review of the literature by experts who then described the elements of a broad research agenda for investigating this technique. If the process that we describe in this paper can guide the acquisition of knowledge in this field, it may serve as a model for evaluating other new technologies before they become widely adopted.

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APPENDIX A

• Expert Panel Members

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