Comparing focused ultrasound and uterine artery embolization for uterine fibroids—rationale and design of the Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) trial

Esther V. A. Bouwsma, M.D.,[a,b] *Gina K. Hesley, M.D.,*[a,c] *David A. Woodrum, M.D., Ph.D.,*[a,c] *Amy L. Weaver, M.S.,*[d] *Phyllis C. Leppert, M.D., Ph.D.,*[e] *Lisa G. Peterson, R.N., M.A.N.,*[a,b] *and Elizabeth A. Stewart, M.D.*[a,b]

[a] Center for Uterine Fibroids, [b] Department of Obstetrics and Gynecology, [c] Department of Radiology, and [d] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; and [e] Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina

Objective: To present the rationale, design, and methodology of the Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) study.
Design: Randomized clinical trial.
Setting: Two academic medical centers.
Patient(s): Premenopausal women with symptomatic uterine fibroids.
Intervention(s): Participants are randomized to two U.S. Food and Drug Administration–approved minimally invasive treatments for uterine leiomyomas: uterine artery embolization and magnetic resonance–guided focused ultrasound.
Main Outcome Measure(s): The primary endpoint is defined as the need for an additional intervention for fibroid symptoms following treatment. Secondary outcomes consist of group differences in symptom alleviation, recovery trajectory, health-related quality of life, impairment of ovarian reserve, treatment complications, and the economic impact of these issues.
Result(s): The trial is currently in the phase of active recruitment.
Conclusion(s): This randomized clinical trial will provide important evidence-based information for patients and health care providers regarding optimal minimally invasive treatment approach for women with symptomatic uterine leiomyomas.
Clinical Trial Registration: NCT00995878. (Fertil Steril® 2011;96:704–10. ©2011 by American Society for Reproductive Medicine.)

Key Words: Leiomyomas, MRgFUS, uterine artery embolization, focused ultrasound, randomized clinical trial, economic analysis

Received May 12, 2011; revised and accepted June 22, 2011; published online July 27, 2011.
G.K.H., D.A.W., P.C.L., L.G.P., and E.A.S. receive support through RC1HD063312 and R01HD060503 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (to E.A.S.). G.K.H., L.G.P., and E.A.S. received salary support for a separate clinical trial agreement between Mayo Clinic and InSightec (Haifa, Israel) for clinical trial NCT00730886. E.A.S. also serves as a consultant to Abbott, Columbia Laboratories, and Gynesonics and serves on the scientific advisory board for the Bayer HealthCare Scientific Committee. EVAB and ALW have nothing to disclose.
Supported by RC1HD063312 and R01HD060503 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (NIH) and NIH/National Center for Research Resources Clinical and Translational Science Awards grant number UL1 RR024150. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.
Reprint requests: Elizabeth A. Stewart, M.D., Mayo Clinic, Department of Obstetrics and Gynecology, 200 First Street, SW, Rochester, Minnesota 55901 (E-mail: stewart.elizabeth@mayo.edu).

Uterine leiomyomas (myomas or fibroids) are benign clonal tumors arising from the uterine myometrium. They are seen in one fourth of all women, and studies note a disproportionate burden of disease for women of African descent (1–5).

Leiomyomas also are important from a health care economics perspective. The direct costs attributable to leiomyomas exceed $2.1 billion annually in the United States (6). Moreover, indirect costs (disability and absenteeism) appear equivalent to direct costs (7).

Despite their clinical and economic importance, there is little evidence on which to base treatment decisions. The 2007 evidence based report concluded: "The dearth of high-quality evidence supporting the effectiveness of most interventions for uterine fibroids is remarkable, given how common this problem is.… Significant research gaps include well-conducted trials in US populations that directly compare interventions on short- and, especially, long-term outcomes" (8).

Hysterectomy has been the major treatment option for uterine fibroids. However, there are several important alternatives to

0015-0282/$36.00
doi:10.1016/j.fertnstert.2011.06.062

TABLE 1

Study objectives.

1	To report comprehensive outcomes and predictors of outcome following leiomyoma treatment with UAE and MRgFUS
2	To provide comprehensive assessment of uterine fibroid symptomatology at baseline and following leiomyoma treatment with UAE and MRgFUS
3	To enhance the study population for black women to allow subgroup analysis
4	To test the reliability of study instruments used to assess fibroid symptomatology when administered during menses compared to other times
5	To quantitate and compare the ovarian impairment following leiomyoma treatment with UAE and MRgFUS
6	To produce an economic analysis of UAE and MRgFUS treatment from a U.S. societal perspective
7	To generate resources that can be used at a later time to assess the biologic and genetic variables affecting treatment outcome

Bouwsma. The FIRSTT trial: rationale and design. Fertil Steril 2011.

hysterectomy. Two minimally invasive therapies are approved by the Food and Drug Administration for treatment of leiomyomas in a variety of locations: uterine artery embolization (UAE) and magnetic resonance–guided focused ultrasound surgery (MRgFUS).

Uterine artery embolization is a minimally invasive angiographic technique causing ischemic fibroid necrosis. It is a global uterine therapy treating the whole uterus and not just individual leiomyomas. Uterine artery embolization has been used since 1995 and is considered a standard treatment for women with no desire for future fertility (9, 10). Numerous studies have demonstrated its effectiveness at 3 to 5 years, and randomized clinical trials have been performed in Europe comparing UAE to surgical therapy (11–17).

Magnetic resonance–guided focused ultrasound surgery provides noninvasive fibroid-specific therapy utilizing high-intensity ultrasonography through the abdominal wall to cause coagulative necrosis in specific fibroids. Guidance and thermal monitoring is provided by dynamic real-time magnetic resonance imaging. Magnetic resonance–guided focused ultrasound surgery was approved by the Food and Drug Administration in 2004 (18). Reports of efficacy of this technique in reducing symptoms have been published (18–26). However, comparative or randomized trials involving MRgFUS have not yet been reported.

MATERIALS AND METHODS

Overview

The Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) study is a randomized clinical trial to evaluate the efficacy of UAE and MRgFUS (NCT00995878, clinicaltrials.gov). The purpose of this manuscript is to describe the rationale, design, and methods of this trial. The FIRSTT trial is conducted at two sites: Mayo Clinic (Rochester, Minnesota) and Duke University (Durham, North Carolina). Women with uterine fibroids, symptoms attributable to these fibroids, and uteruses where abdominal surgery would be considered the standard of care will be randomized to either UAE or MRgFUS. Over a 48-month enrollment period, started January 2010, 220 eligible respondents will be enrolled and randomized. The Institutional Review Board at each institution approved the same study protocol.

The primary objective of the FIRSTT trial is to provide evidence-based guidance to women with uterine leiomyomas and health care providers. The primary endpoint is the need for any additional medical or surgical intervention for fibroid symptoms, because this is what most women see as the goal of treatment. This will be supplemented by assessment of general and health-specific quality of life measures. The study attempts to balance scientific rigor without making the protocol so onerous to adversely impact recruitment.

Given the paucity of information on uterine leiomyomas, multiple secondary endpoints are included in the trial design. Extensive assessment of baseline symptoms will be conducted using validated measures for other diseases never applied to uterine leiomyomas, including such standard measures as the McGill Pain Questionnaire (27). A diary system will track recovery trajectory, adverse events, and medication use for each treatment option.

Moreover, an economic analysis will be conducted from a societal perspective. Although women are censored for efficacy outcomes when they undergo another medical or surgical procedure for uterine fibroids, all women will be followed for 3 years to understand the costs of both effective and ineffective primary therapy.

Evaluation occurs at 2, 4, and 6 weeks; 6 months; and 1, 2, and 3 years. At the outset, the study follow-up was only funded through the 6-month time point via the American Recovery and Reinvestment Act of 2009. However, the initial consent form stated 36-month funding was being sought so only a minor protocol modification was needed after additional funding was achieved.

Serum is collected at baseline and yearly intervals to allow assessment of ovarian reserve following treatment. A group of control women will also be recruited for assessment of ovarian reserve. DNA is also collected at baseline to allow future studies. For women failing initial treatment (UAE or MRgFUS) and going on to surgical therapy, analysis of excised tissue will be conducted. Table 1 lists all study objectives.

Study Population

All women will be premenopausal with symptoms that appear attributable to uterine fibroids. Prior to being considered for study entry, each potential subject has a complete gynecologic evaluation by a study physician to exclude women with concomitant issues including oligoovulation, bleeding disorders, and endometrial polyps. Women who are candidates for the levonorgestrel intrauterine system, endometrial ablation, or hysteroscopic myomectomy are not enrolled for the FIRSTT study.

Women with prior leiomyoma treatment are excluded to avoid biasing the sample toward women with a higher risk of recurrent, undertreated, or untreated leiomyomas. Subjects must have uteruses of 20 gestational weeks in size or smaller, and initial enrollment criteria excluded all myomas greater than 10 cm. In January 2011, the enrollment criteria were revised by investigators at both sites on the basis of current experience with MRgFUS. The limitation of a single leiomyoma greater than 10 cm was replaced with more than six leiomyomas greater than 3 cm in maximal diameter. None of the previously treated subjects would have been excluded by this change. Contraindications to UAE (allergy to iodinated contrast or use of GnRH analogs) or MRgFUS (gadolinium allergy, implanted metallic device, or severe claustrophobia) also serve as exclusion criteria. Table 2 presents all inclusion and exclusion criteria.

Enhancing the study population for Black women is an important objective of our study. First, women of African descent are the most severely affected by the disease, having an increased incidence and relative risk of fibroids, an earlier onset of disease, and more severe symptoms (1–3, 5). Second, despite their increased risk of disease, Black women historically comprise only approximately 15% of subjects in fibroid studies (28).

TABLE 2

Inclusion and exclusion criteria.

Inclusion criteria	Women able to give informed consent and willing and able to attend all study visits
	Premenopausal women at least 25 years of age
	No evidence of high-grade SILs by pap smears or HPV testing within institutional guidelines
Exclusion criteria	Women actively trying for pregnancy or currently pregnant
	Uterine size >20 weeks' gestation
	Prior myomectomy, UAE, or MRgFUS
	More than six fibroids >3 cm in maximum diameter
	Allergy to either gadolinium or iodinated contrast
	Implanted metallic device prohibiting MRI
	Severe claustrophobia
	Active pelvic infection
	Intrauterine contraceptive device in place at the time of treatment
	Severe abdominal scarring precluding safe MRgFUS treatment
	BMI that prohibits subject from fitting in MRI device
	Current use of GnRH agonists or antagonists
	Unstable medical conditions requiring additional monitoring during the procedure
	Bleeding diathesis requiring medical treatment
	MRI suggestive of malignant disease of uterus, ovary, or cervix
	MRI showing only adenomyosis
	MRI with pedunculated submucosal or subserosal myoma with a stalk less than 25% of the maximal fibroid diameter
	No enhancement of leiomyoma with gadolinium

Note: SIL = squamous intraepithelial lesion; HPV = human papilloma virus; MRI = magnetic resonance imaging.

Bouwsma. The FIRSTT trial: rationale and design. Fertil Steril 2011.

Women desiring childbearing The criterion standard for treatment of symptomatic fibroids in women who wish to preserve fertility is surgical myomectomy (10). However, there is reproductive morbidity to myomectomy that can contribute to infertility (29). Although both UAE and MRgFUS may cause morbidity among women desiring pregnancy, both techniques have resulted in successful pregnancies (30, 31). Because of the lack of evidence of serious obstetric adverse effects and respect for subject autonomy, women interested in future pregnancy will not be excluded from our trial. However, they will be counseled that there are potential risks of these treatments for future pregnancies. However, women seeking fertility enhancement will be excluded.

Comorbidity Women with significant medical issues are not excluded because they are likely to benefit from nonsurgical alternatives. The two exclusions for medical comorbidities are women with unstable conditions requiring additional monitoring during the procedure because neither treatment uses anesthesia personnel for monitoring and women with bleeding diathesis requiring medical treatment that would adversely impact UAE treatment but not MRgFUS.

Recruitment Strategies

The FIRSTT trial employs traditional recruitment strategies including letters to referring clinicians, booths, posters, and Internet postings at www.clinicaltrials.gov and www.mayo.org. Of the first 200 women contacting the study, 75% learned about the study through the Internet (32). This percentage is consistent with the results of other leiomyoma studies (33, 34).

We have updated our strategy to include social media, including a Facebook Fibroid Study Group (http://on.fb.me/gewuoO). We are also exploring the possibilities to target specific patient groups through social media.

Assessment before Treatment

A pelvic magnetic resonance imaging with IV gadolinium contrast is conducted before treatment to define leiomyomas by number, volume, location, signal characteristics, and enhancement. To facilitate enrollment, outside magnetic resonance images are reviewed at each site. Imaging criteria exclude women with findings suspicious for malignancy.

Baseline questionnaires assess demographic, anthropometric, and reproductive variables shown to affect leiomyoma formation or recurrence. The Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QOL), a disease-specific quality of life measure, is administered (35). Although many studies require a minimum UFS-QOL score for study enrollment, the FIRSTT study does not. Our prior experience showed that some severely symptomatic women, such as those with recurrent urinary obstruction, are not captured with this instrument. A series of other validated instruments will be used to assess menstrual distress (Menstrual Distress Questionnaire), menorrhagia (Aberdeen Menorrhagia Clinical Outcomes Questionnaire), general health (RAND Medical Outcomes Trust Study Short Form–36), presence of depression (Center for Epidemiologic Studies Depression Scale), sexual function (Female Sexual Function Index), and pain (McGill Pain Questionnaire and Visual Analog Scale) (27, 36–41). As vitamin D has recently been postulated to play a role in fibroid pathogenies, a validated sun-exposure questionnaire is also used (42, 43). Baseline assessments will take place during menstrual flow and approximately 2 weeks later to distinguish issues such as noncyclic pelvic pain from dysmenorrhea. Table 3 provides a schedule of all assessments. Table 4 summarizes all validated questionnaires used.

Randomization

The randomization scheme will be stratified by participating center and uterine volume calculated from pretreatment magnetic resonance imaging because earlier studies suggest that UAE outcome is significantly affected by uterine size (12). We use a cutoff of 700 cm^3, which is similar to the median in previous studies (12). Randomization will be conducted using small (4–8) varied permuted block size to mitigate any significant time trend for treatment innovation and minimize ascertainment bias. After randomization, every attempt to treat the subject within 10 days will be made to minimize the chance of losing subjects.

TABLE 3

Schedule of assessments.

	Enrollment (menses)	Non-menses assessment	Treatment	2 wk	4 wk	6 wk	6 mo	12 mo	24 mo	36 mo
Study visit	•		•					•	•	•
Informed consent	•									
Request for medical records	•						•	•	•	•
Phone follow-up		•		•	•	•	•			
MRI assessment	•							•	•	•
Phlebotomy	•							•	•	•
Storage of DNA	•									
Baseline questionnaire	•									
Symptom assessment	•						•	•	•	•
UFS-QOL[a]	•	•				•	•	•	•	•
SF-36	•	•				•	•	•	•	•
CES-D	•	•					•	•	•	•
MPQ and VAS	•	•	•			•	•	•	•	•
MDQ	•						•	•	•	•
AMCOQ	•						•	•	•	•
FSFI	•	•					•	•	•	•
Sun Exposure Questionnaire	•									
Short-term outcomes diary				•	•	•				
Assessment of treatment variables			•							
Adverse events			•			•	•	•	•	•
Long-term outcomes							•	•	•	•
Economic assessment	•		•	•	•	•	•	•	•	•
Medical records review						•		•	•	•
Study stipend			•			•	•	•	•	•

Note: MRI = magnetic resonance imaging.

[a] For all abbreviated scale names, please refer to Table 4.

Bouwsma. The FIRSTT trial: rationale and design. Fertil Steril 2011.

Uterine Artery Embolization Procedure

Patients randomized to UAE will undergo a standardized treatment protocol. An IV line and Foley catheter will be placed and the patient receives conscious sedation, antiinflammatory agents, antiemetics, and antibiotic prophylaxis during the procedure.

Via the right common femoral artery, an arteriogram is performed to visualize the pelvic vasculature with notation of whether any branches of the ovarian artery are supplying the fibroids. Embolization to near stasis is performed from the contralateral uterine artery followed by the same process from the ipsilateral side. Subjects are observed for 60 minutes in a recovery room and are subsequently hospitalized overnight for pain control with a variety of agents, including narcotics via a patient-controlled device, nonsteroidal antiinflammatory drugs, and adjunctive agents, including antiemetics.

Magnetic Resonance–Guided Focused Ultrasound Procedure

Patients undergoing MRgFUS are treated as outpatients with a standardized procedure. Women are instructed to shave hair from the umbilicus to the pubic crest the night before treatment. After placing an IV line and a Foley catheter, the patient is positioned prone on the magnetic resonance imaging table with her uterus directly above the focused ultrasonographic transducer. Abdominal wall scars are noted.

During the procedure, IV conscious sedation is used, however, allowing communication with the treating physician to report any symptoms. Patients in the MRgFUS arm are typically observed for 1 hour after their last dose of sedation and discharged to home with an escort.

Management after Procedure

In the recovery area, subjects are asked to rate their discomfort and pain on a 10-point continuous scale and the McGill Pain Questionnaire. At the time of discharge, all women are given prescriptions for ibuprofen, oxycodone, prochlorperazine (Compazine), and docusate (Colace) in standard doses and amounts to use as necessary. Short-term outcome diaries are used for 6 weeks following the procedure to assess disability and recovery trajectory.

Adverse events are recorded and are similar to those used in UAE studies but updated to reflect earlier hospital discharge patterns (44). At 6 weeks and annually thereafter, a medical record review will be conducted to capture any unreported events. A multidisciplinary Data Safety and Monitoring Board will monitor the trial.

A long-term questionnaire will assess treatment outcomes at 6, 12, 24, and 36 months after the procedure. This instrument appraises the return of any fibroid symptoms and assesses disruption of menstrual cyclicity. Moreover, it assesses any new or alternative therapies used to treat these symptoms and any evidence of reproductive dysfunction.

A magnetic resonance imaging will be performed at 24 and 36 months to compare the volume of the uterus and each fibroid before and after the treatment. The nonperfused volume for treated fibroids, a noninvasive measure of tissue necrosis, will be monitored and any new fibroids developing during this follow-up interval will be measured.

Ovarian Impairment

There is concern that UAE affects ovarian function because it causes an age-related increase in amenorrhea rates following treatment (9, 44–49). However, not only UAE but also hysterectomy and myomectomy have

TABLE 4

Validated questionnaires.

Questionnaire	Assessment	Description
Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QOL)	Symptom severity and HRQL	Eight-item Symptom Severity Scale (SSS) and 29 HRQL items comprising six domains: concern, activities, energy/mood, control, self-consciousness, and sexual function. Symptom severity and HRQL subscale scores are summed and transformed into a 0–100-point scale.
Medical Outcomes Trust Study Short Form–36 (SF-36)	General health status	Thirty-six items composed of eight domains: physical function, role limitations (physical), vitality, general health perceptions, bodily pain, social function, role limitations (emotional), and mental health.
Center for Epidemiologic Studies Depression Scale (CES-D)	Presence of current depression	Twenty symptoms of depression, comprising 16 negative items and 4 positive items.
Menstrual Distress Questionnaire (MDQ)	Menstrual distress	Forty-seven items to distinguish cyclical from noncyclical changes in physical symptoms, mood, behavior, and arousal.
Aberdeen Menorrhagia Clinical Outcomes Questionnaire (AMCOQ)	Menstrual bleeding	Thirteen questions on duration of period and menstrual cycle, amount of menstrual flow, pain related to menstrual flow, and the effort of symptoms on daily activities. Responses are converted to a single menorrhagia severity score between 0 and 100.
McGill Pain Questionnaire (MPQ)	Pain	Twenty groups of words to describe three attributes of pain (affective, evaluative, and sensory) that then allow computation of both the pain rating index and the present pain intensity.
Visual Analog Scale (VAS)	Pain	Ten-centimeter horizontal line with the two endpoints labeled "no pain" and "worst pain ever." Patients are required to place a mark on the 10-cm line at a point that corresponds to the level of pain intensity they feel. The distance in centimeters is used as a numerical index of the severity of pain.
Female Sexual Function Index (FSFI)	Sexual function	Nine-item questionnaire, grouped into six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain).
Sun Exposure Questionnaire	Sun exposure	Forty-two questions to quantify the number of hours exposed to sun during age-specific activities in four age categories.

Note: HRQL = health-related quality of life.

Bouwsma. The FIRSTT trial: rationale and design. Fertil Steril 2011.

been documented to cause ovarian impairment demonstrated by an increase in FSH or a decline in ovarian antimüllerian hormone greater than that seen with aging (17, 50–52).

Thus, determining if ovarian impairment is inherent to all myoma therapies is a critical goal of the FIRSTT trial. Although the introduction of amenorrhea can be beneficial for perimenopausal women, for young women who desire fertility, amenorrhea is a significant adverse event. Early follicular phase serum will be collected from women participating in the FIRSTT trial at baseline and at 12, 24, and 36 months after treatment.

Economic Analysis

An economic analysis of UAE and MRgFUS treatment will be conducted from a U.S. societal perspective by determining disease-specific resource use (including both direct medical and nonmedical costs and indirect costs) and a cost-effectiveness analysis assessing the incremental mean costs per quality-adjusted life year with each therapy. Data on resource use at the level of the patient will include many costs for products and services previously not captured, including costs of sanitary products, over-the-counter medications and supplements, and alternative and complementary therapies. Indirect costs will be estimated using data on lost work days and days with ability limitations. Procedural and postprocedural costs of care are prospectively collected starting at the time the patient is admitted to the hospital until the time of discharge. Moreover, all interventions (both medical and surgical) for the entire 36 months that occur after initial treatment are recorded, including the intervention-free interval.

Data Management and Statistical Analysis

The FIRSTT study is powered to detect the anticipated differences in clinical outcomes with a type I error level of 5%, assuming a 10% dropout rate for subjects. An intention to treat analysis will be conducted. The cumulative incidence of needing an additional intervention will be estimated using the Kaplan-Meier method, separately for each treatment group. A Cox proportional hazard regression models will be fit to evaluate the association between

type of treatment (UAE vs. FUS) and the need for an additional intervention within 36 months.

For analysis of symptom and QOL scores, ordinary linear regression models will be fit to evaluate the association between treatment type and scores at 12, 24, and 36 months, respectively. The fore-mentioned models will be adjusted for the baseline score by including it as a covariate. In addition, models will also be fit using the delta scores as the endpoint, where delta is the difference in scores at follow-up and baseline. Additional univariate and multivariate models will be fit separately for each treatment group to identify factors associated with change in symptom and QOL scores. The subsequent scores for subjects who have had an additional surgery will be imputed using the last-value-carry-forward approach; thus, women who have poor scores and change treatments as a result will not be removed from the analysis at subsequent time points. In contrast to most previous studies, subjects experiencing menopause will be censored at the date of their last menstrual period before 1 year of amenorrhea.

For study instruments administered longitudinally, scores will also be analyzed using a repeated measures model to assess each subject's score trajectory over time using all available scores. The repeated measures analyses will be evaluated using linear mixed models, and the correlation between the repeated measures per subject will be handled by specifying an unstructured covariance matrix.

Partnerships to Extend Access

To increase enrollment and the economic diversity of enrollees, we have explored several partnerships. We have approached manufacturers of devices used in both procedures to provide resources to allow more women to enroll. A successful agreement was reached with the manufacturer of the FUS equipment (InSightec, Haifa, Israel) to provide a safety net for enrolling women. If the woman is insured, the study agrees to pursue insurance appeals for coverage; however, final payment of treatment costs will be assumed under an unrestricted grant from industry sources.

We are also actively pursuing governmental and foundation funding to provide coverage for uninsured women. Although we have not achieved this goal at the time this article was written, pursuit of this critical goal is ongoing.

DISCUSSION

We believe the FIRSTT trial is an important randomized clinical trial with a unique design in an understudied area critical to women's health. The study aims to provide evidence-based data on the safety and efficacy of UAE and MRgFUS and provide a large pool of information intensely needed to fill in current gaps in knowledge about fibroid symptomatology and treatment. Baseline symptomatology will be comprehensively assessed using both validated instruments for women with fibroids and validated measures for other diseases never applied to uterine leiomyoma. Assessing symptoms at different times in the menstrual cycles has also never been done previously for most leiomyoma issues. Understanding baseline symptomatology will help identify clinical predictors of success, to assist clinicians in choosing the most optimal minimally invasive treatment approach for their patients.

Another major strength in this study's design is our effort to enhance the study population for black women. Conducting the study at the two different sites adds important geographic diversity. Enrollment of sufficient African American women will allow subgroup analysis, addressing the observed great racial disparity of uterine fibroids. Current studies suggest that black women have different genes or different polymorphisms in known genes than white women with fibroids (53–55) and as genotyping is underway, the collection of biological resources for future research will prove its value with time.

Censoring women at the time of menopause is another key feature. UAE is associated with high amenorrhea rates after treatment, and the fact that heavy menstrual bleeding is a major predictor of successful outcome leads to the hypothesis that some of the symptomatic improvement following UAE is confounded by amenorrhea. In addition, assessment of ovarian impairment following myoma therapies is essential. A strong point in our study is that we not only assess menstrual cyclicity following treatment but also measure FSH and antimüllerian hormone levels at baseline and annually thereafter.

Because many women have access to Internet and use it to find information about alternatives to hysterectomy, we believe in the potential role of social media in recruitment strategies. The Facebook group specifically for the FIRSTT trial is an example of our innovative design.

Finally, the economic implication of uterine fibroids is enormous. However, currently there are no direct economic comparisons of MRgFUS and UAE and no evaluations from the societal perspective of either treatment based on cost assumptions within the U.S. system. In our analysis, we will include direct medical costs, costs to the patient, as well as indirect costs in an attempt to provide a comprehensive but surrogate measure of societal costs.

The main issue facing the FIRSTT trial is obtaining sufficient enrollment. An observed problem is that many insurance companies still consider MRgFUS as an experimental therapy and, therefore, do not cover the costs of treatment. Because of declined reimbursement, a considerable number of otherwise eligible patients cannot be enrolled in our study. Taran et al. conducted a survey on the first Focused Ultrasound Symposium in 2008 and reported that the mean percentage of patients eligible for treatment but not receiving therapy because of declined reimbursement was reported to be 81% ± 19% (range 40%–100%) (56).

REFERENCES

1. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997;90:967–73.
2. Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med 1996;41:483–90.
3. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7.
4. Stewart EA. Uterine fibroids. Lancet 2001;357:293–8.
5. Huyck KL, Panhuysen CI, Cuenco KT, Zhang J, Goldhammer H, Jones ES, et al. The impact of race as a risk factor for symptom severity and age at diagnosis of uterine leiomyomata among affected sisters. Am J Obstet Gynecol 2008;198:168.e1–9.
6. Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. Am J Obstet Gynecol 2006;195:955–64.
7. Lee DW, Gibson TB, Carls GS, Ozminkowski RJ, Wang S, Stewart EA. Uterine fibroid treatment patterns in a population of insured women. Fertil Steril 2009;91:566–74.
8. Viswanathan M, Hartmann K, McKoy N, Stuart G, Rankins N, Thieda P, et al. Management of uterine fibroids: an update of the evidence. Evid Report Technol Assess; 2007:1–122.
9. Ravina JH, Herbreteau D, Ciraru-Vigneron N, Bouret JM, Houdart E, Aymard A, et al. Arterial embolisation to treat uterine myomata. Lancet 1995;346:671–2.
10. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol 2008;112:387–400.
11. Goodwin SC, Spies JB, Worthington-Kirsch R, Peterson E, Pron G, Li S, et al. Uterine artery embolization for treatment of leiomyomata: long-term outcomes from the FIBROID Registry. Obstet Gynecol 2008;111:22–33.
12. Spies JB, Bruno J, Czeyda-Pommersheim F, Magee ST, Ascher SA, Jha RC. Long-term outcome of uterine artery embolization of leiomyomata. Obstet Gynecol 2005;106:933–9.

13. Hehenkamp WJ, Volkers NA, Donderwinkel PF, de Blok S, Birnie E, Ankum WM, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial. Am J Obstet Gynecol 2005;193: 1618–29.
14. Gupta J, Sinha A, Lumsden M, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev; 2006:CD005073.
15. Mara M, Fucikova Z, Maskova J, Kuzel D, Haakova L. Uterine fibroid embolization versus myomectomy in women wishing to preserve fertility: preliminary results of a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2006; 126:226–33.
16. Edwards RD, Moss JG, Lumsden MA, Wu O, Murray LS, Twaddle S, et al. Uterine-artery embolization versus surgery for symptomatic uterine fibroids. N Engl J Med 2007;356:360–70.
17. Hehenkamp WJ, Volkers NA, Broekmans FJ, de Jong FH, Themmen AP, Birnie E, et al. Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy. Hum Reprod 2007;22:1996–2005.
18. Stewart EA, Gostout B, Rabinovici J, Kim HS, Regan L, Tempany CM. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. Obstet Gynecol 2007;110:279–87.
19. Hesley GK, Felmlee JP, Gebhart JB, Dunagan KT, Gorny KR, Kesler JB, et al. Noninvasive treatment of uterine fibroids: early Mayo Clinic experience with magnetic resonance imaging-guided focused ultrasound. Mayo Clin Proc 2006;81:936–42.
20. Fennessy FM, Tempany CM, McDannold NJ, So MJ, Hesley G, Gostout B, et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery—results of different treatment protocols. Radiology 2007;243:885–93.
21. Rabinovici J, Inbar Y, Revel A, Zalel Y, Gomori JM, Itzchak Y, et al. Clinical improvement and shrinkage of uterine fibroids after thermal ablation by magnetic resonance-guided focused ultrasound surgery. Ultrasound Obstet Gynecol 2007;30:771–7.
22. Morita Y, Ito N, Hikida H, Takeuchi S, Nakamura K, Ohashi H. Non-invasive magnetic resonance imaging-guided focused ultrasound treatment for uterine fibroids—early experience. Eur J Obstet Gynecol Reprod Biol 2007;139:199–203.
23. Morita Y, Takeuchi S, Hikida H, Ohashi H, Ito N. Decreasing margins to the uterine serosa as a method for increasing the volume of fibroids ablated with magnetic resonance-guided focused ultrasound surgery. Eur J Obstet Gynecol Reprod Biol 2009;146: 92–5.
24. Funaki K, Fukunishi H, Sawada K. Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. Ultrasound Obstet Gynecol 2009;34:584–9.
25. Zaher S, Gedroyc WM, Regan L. Patient suitability for magnetic resonance guided focused ultrasound surgery of uterine fibroids. Eur J Obstet Gynecol Reprod Biol 2009;143:98–102.
26. LeBlang SD, Hoctor K, Steinberg FL. Leiomyoma shrinkage after MRI-guided focused ultrasound treatment: report of 80 patients. AJR Am J Roentgenol 2010;194:274–80.
27. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–99.
28. Taran FA, Brown HL, Stewart EA. Racial diversity in uterine leiomyoma clinical studies. Fertil Steril 2010;94:1500–3.
29. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91:1215–23.
30. Homer H, Saridogan E. Uterine artery embolization for fibroids is associated with an increased risk of miscarriage. Fertil Steril 2010;94:324–30.
31. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril 2010;93:199–209.
32. Bouwsma E, Peterson L, Stewart E. The Internet as a key recruitment strategy in leiomyoma clinical trials. Washington, D.C.: American College of Obstetricians and Gynecologists; 2011.
33. Ankem K. Information-seeking behavior of women in their path to an innovative alternate treatment for symptomatic uterine fibroids. J Med Libr Assoc 2007;95:164–72, e51–3.
34. McCarthy-Keith D, Nurudeen S, Armstrong A, Levens E, Nieman LK. Recruitment and retention of women for clinical leiomyoma trials. Contemp Clin Trials 2010;31:44–8.
35. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol 2002;99:290–300.
36. Moos RH. The development of a menstrual distress questionnaire. Psychosom Med 1968;30:853–67.
37. Ruta DA, Garratt AM, Chadha YC, Flett GM, Hall MH, Russell IT. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? Qual Life Res 1995;4:33–40.
38. Ruta DA, Garratt AM, Russell IT. Patient centred assessment of quality of life for patients with four common conditions. Qual Health Care 1999;8:22–9.
39. Hays RD, Sherbourne CD, Mazel R. User's manual for the Medical Outcomes Study (MOS) core measures of health-related quality of life. Durham, NC: Duke University Press; 1992.
40. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol 1977;106:203–14.
41. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marit Ther 2000;26:191–208.
42. Zaitseva M, Vollenhoven BJ, Rogers PA. Retinoids regulate genes involved in retinoic acid synthesis and transport in human myometrial and fibroid smooth muscle cells. Hum Reprod 2008;23:1076–86.
43. Halder SK, Goodwin JS, Al-Hendy A. 1,25-Dihydroxyvitamin D3 reduces TGF-β3-induced fibrosis-related gene expression in human uterine leiomyoma cells. J Clin Endocrinol Metab 2011;96:E754–62.
44. Spies JB, Spector A, Roth AR, Baker CM, Mauro L, Murphy-Skrynarz K. Complications after uterine artery embolization for leiomyomas. Obstet Gynecol 2002;100:873–80.
45. Pelage JP, Le Dref O, Soyer P, Kardache M, Dahan H, Abitbol M, et al. Fibroid-related menorrhagia: treatment with superselective embolization of the uterine arteries and midterm follow-up. Radiology 2000;215:428–31.
46. Spies JB, Roth AR, Gonsalves SM, Murphy-Skrzyniarz KM. Ovarian function after uterine artery embolization for leiomyomata: assessment with use of serum follicle stimulating hormone assay. J Vasc Interv Radiol 2001;12:437–42.
47. Pron G, Bennett J, Common A, Wall J, Asch M, Sniderman K. The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. Fertil Steril 2003;79:120–7.
48. Pron G, Mocarski E, Bennett J, Vilos G, Common A, Vanderburgh L. Pregnancy after uterine artery embolization for leiomyomata: the Ontario multicenter trial. Obstet Gynecol 2005;105:67–76.
49. Walker WJ, Barton-Smith P. Long-term follow up of uterine artery embolisation—an effective alternative in the treatment of fibroids. Br J Obstet Gynaecol 2006;113:464–8.
50. Tulandi T, Sammour A, Valenti D, Child TJ, Seti L, Tan SL. Ovarian reserve after uterine artery embolization for leiomyomata. Fertil Steril 2002;78:197–8.
51. Chan CC, Ng EH, Ho PC. Ovarian changes after abdominal hysterectomy for benign conditions. J Soc Gynecol Investig 2005;12:54–7.
52. Kim HS, Tsai J, Lee JM, Vang R, Griffith JG, Wallach EE. Effects of utero-ovarian anastomoses on basal follicle-stimulating hormone level change after uterine artery embolization with tris-acryl gelatin microspheres. J Vasc Interv Radiol 2006;17: 965–71.
53. Gross KL, Panhuysen CI, Kleinman MS, Goldhammer H, Jones ES, Nassery N, et al. Involvement of fumarate hydratase in nonsyndromic uterine leiomyomas: genetic linkage analysis and FISH studies. Genes Chromosomes Cancer 2004;41:183–90.
54. Al-Hendy A, Salama SA. Catechol-*O*-methyltransferase polymorphism is associated with increased uterine leiomyoma risk in different ethnic groups. J Soc Gynecol Investig 2006;13:136–44.
55. Al-Hendy A, Salama SA. Ethnic distribution of estrogen receptor-alpha polymorphism is associated with a higher prevalence of uterine leiomyomas in black Americans. Fertil Steril 2006;86:686–93.
56. Taran FA, Hesley GK, Gorny KR, Stewart EA. What factors currently limit magnetic resonance-guided focused ultrasound of leiomyomas? A survey conducted at the first international symposium devoted to clinical magnetic resonance-guided focused ultrasound. Fertil Steril 2010;94:331–4.