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Comparing focused ultrasound and uterine artery embolization for uterine fibroids – Rationale and Design of the Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) trial

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Abstract

Objective—To present the rational, design and methodology of the FIRSTT study (Fibroid Interventions: Reducing Symptoms Today and Tomorrow, NCT00995878, clinicaltrials.gov).

Design—Randomized Clinical Trial (RCT)

Setting—Two Academic Medical Centers

Patient(s)—Premenopausal women with symptomatic uterine fibroids.

Intervention(s)—Participants are randomized to two FDA-approved minimally invasive treatments for uterine leiomyomas: uterine artery embolization (UAE) and MRI guided focused ultrasound (MRgFUS).

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.

Results—The trial is currently in the phase of active recruitment.

Conclusions—This RCT will provide important evidence-based information for patients and health care providers regarding optimal minimally invasive treatment approach for women with symptomatic uterine leiomyomas.

Keywords

leiomyomas; MRgFUS; uterine artery embolization; focused ultrasound; randomized clinical trial; economic analysis

INTRODUCTION

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 healthcare 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 hysterectomy. Two minimally invasive therapies are approved by the Food and Drug Administration (FDA) for treatment of leiomyomas in a variety of locations: Uterine Artery Embolization (UAE) and Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS).

UAE 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. UAE 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 efficacy at three to five years and randomized clinical trials (RCTs) have been performed in Europe comparing UAE to surgical therapy (11–17).

MRgFUS provides noninvasive fibroid-specific therapy utilizing high intensity ultrasound through the abdominal wall to cause coagulative necrosis in specific fibroids. Guidance and thermal monitoring is provided by dynamic real-time MR imaging. MRgFUS was FDA-approved 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 RCT 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, MN) and Duke University

(Durham, NC). Women with uterine fibroids, symptoms attributable to these fibroids and uteri 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 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, since 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 (MPQ)(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 three 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. Woman who are candidates for the levonorgestrel intrauterine system, endometrial ablation, or hysteroscopic myomectomy are not considered to be candidates 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 uteri of 20 gestational weeks in size or smaller and initial enrollment criteria excluded all myomas greater than 10 centimeters. In January of 2011, the enrollment criteria were revised by investigators at both sites based on current experience with MRgFUS. The limitation of a single leiomyoma greater than 10 centimeters was replaced with more than 6 leiomyomas greater than 3 centimeters 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). Secondly, despite their increased risk of disease, Black women historically comprise only approximately 15% of subjects in fibroid studies (28).

Women desiring childbearing—The “gold-standard” for treatment of symptomatic fibroids in women who wish to preserve fertility is surgical myomectomy (10). However, there is reproductive morbidity to myomectomy which can contribute to infertility (29). While both UAE and MRgFUS may have morbidity for 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 since they are likely to benefit from nonsurgical alternatives. The two exclusions for medical comorbidities are women with an unstable conditions requiring additional monitoring during the procedure since neither treatment utilizes anesthesia personnel for monitoring and women with bleeding diathesis requiring medical treatment which 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 two hundred 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 (URL:<http://on.fb.me/gewuoO>). We are also exploring the possibilities to target specific patient groups through social media.

Pre-treatment assessment

A pelvic MRI with intravenous gadolinium contrast is conducted prior to treatment to define leiomyomas by number, volume, location, signal characteristics, and enhancement. To facilitate enrollment, outside MR 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). While many studies require a minimum UFS-QOL score for study enrollment, the FIRSTT study does not. Our prior experience found 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 (MDQ), menorrhagia (AMCOQ), general health (RAND SF-36), presence of depression (CES-D), sexual function (FSFI), and pain (McGill and VAS)(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 at approximately two 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 MR imaging since prior studies suggest UAE outcome is significantly affected by uterine size (12). We use a cutoff of 700 cc³ 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 in order to minimize the chance of losing subjects.

Uterine Artery Embolization Procedure

Patients randomized to UAE will undergo a standardized treatment protocol. An intravenous line and Foley catheter will be placed and the patient receives conscious sedation, anti-inflammatory agents, anti-emetics 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 (PCA), NSAIDs, and adjunctive agents, including anti-emetics.

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 intravenous line and a Foley catheter, the patient is positioned prone on the MRI table with her uterus directly above the FUS-transducer. Abdominal wall scars are noted.

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

Post-procedure management

In the recovery area subjects are asked to rate their discomfort and pain on a 10-point continuous scale and the MPQ. At the time of discharge all women are given prescriptions for ibuprofen, oxycodone, compazine and colace in standard doses and amounts to use as necessary. Short-term outcome diaries are used for six 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 six weeks and annually thereafter, a medical record review will be conducted to capture any unreported events. A multidisciplinary Data Safety and Monitoring Board (DSMB) will monitor the trial.

A long-term questionnaire will assess treatment outcomes at 6-, 12-, 24-, and 36 months post 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 MRI will be performed at 24- and 36-months to compare the volume of the uterus and each fibroid before and after the treatment. The non perfused volume (NPV) for treated fibroids, a noninvasive measure of tissue necrosis will be followed and any new fibroids developing during this follow-up interval will be measured.

Ovarian impairment

There is concern that UAE affects ovarian function since it causes an age-related increase in amenorrhea rates following treatment (9, 44–49). However, not only UAE but also hysterectomy and myomectomy have been documented to cause ovarian impairment demonstrated by an increase in follicle stimulating hormone (FSH) or a decline in ovarian antimüllerian hormone (AMH) 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. While 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 at 12-, 24-, and 36 month following 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 utilization (including both direct medical and non-medical costs and indirect costs) and a cost-effectiveness analysis assessing the incremental mean costs per quality-adjusted life with each therapy. Data on resource utilization 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 by data on lost work days and days with ability limitations. Procedural and post-procedural 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 as surgical) for the entire 36 months which occur following 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 1 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 prior to one 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 utilized 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 manuscript was written, pursuit of this critical goal is ongoing.

DISCUSSION

We believe the FIRSTT-trial is an important RCT 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 identifying 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 geographical 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 following treatment, and the fact that heavy menstrual bleeding is a major predictor of successful outcome, raises the hypothesis that some of the symptomatic improvement following UAE is confounded by amenorrhea. Moreover, assessment of ovarian impairment following myomatherapies is essential. A strong point in our study is the fact that we not only assess menstrual cyclicity following treatment, but also measure FSH and AMH levels at baseline and annually thereafter.

As 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 US 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 the fact that many insurance companies still consider MRgFUS as an experimental therapy, and therefore don't cover the costs of treatment. Due to 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 the mean percentage of patients eligible for treatment not receiving therapy due to declined reimbursement was reported to be $81 \pm 19\%$ (range 40% to 100%) (56).

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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 which can be used at a later time to assess the biologic and genetic variables affecting treatment outcome

Table 2**Inclusion and Exclusion criteria**

<u>Inclusion criteria:</u>	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 Grades SIL by pap smears or HPV testing within institutional guidelines
<u>Exclusion criteria:</u>	Women actively trying for pregnancy or currently pregnant
	Uterine size > 20 weeks
	Prior myomectomy, UAE, or MRgFUS
	More than 6 fibroids > than 3 centimeters in maximal 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 which 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

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	•	•				•	•	•	•	•
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			•			•	•	•	•	•

Table 4

Validated Questionnaires

Questionnaire	Assessment	Description
Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QOL)	Symptom severity and health-related quality of life (HRQL)	8-item Symptom Severity Scale (SSS) and 29 HRQL-items comprising 6 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	36 items comprised 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	20 symptoms of depression, comprising 16 negative items and four positive items.
Menstrual Distress Questionnaire (MDQ)	Menstrual distress	47 items to distinguish cyclical from non-cyclical changes in physical symptoms, mood, behavior, and arousal
Aberdeen Menorrhagia Clinical Outcomes Questionnaire (AMCOQ)	Menstrual bleeding	13 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	20 groups of words to describe three attributes of pain (affective, evaluative and sensory) which then allow computation of both the pain rating index and the present pain intensity
Visual Analog Scale (VAS)	Pain	10-cm 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	9-item questionnaire, grouped into six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain)
Sun Exposure Questionnaire	Sun exposure	42 questions to quantify the number of hours exposed to sun during age specific activities in 4 age categories.