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Fibroid Interventions: Reducing Symptoms Today and Tomorrow: Extending Generalizability by Using a Comprehensive Cohort Design With a Randomized Controlled Trial

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Abstract

Background—Uterine fibroids are an important source of morbidity for reproductive-aged women. Despite an increasing number of alternatives, hysterectomies account for about 75% of all fibroid interventional treatments. Evidence is lacking to help women and their health care providers decide among alternatives to hysterectomy. Fibroid Interventions: Reducing Symptoms Today and Tomorrow (NCT00995878, clinicaltrials.gov) is a randomized controlled trial to compare the safety, efficacy, and economics of 2 minimally invasive alternatives to hysterectomy:

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uterine artery embolization and magnetic resonance imaging–guided focused ultrasound surgery. Although randomized trials provide the highest level of evidence, they have been difficult to conduct in the United States for interventional fibroid treatments. Thus, contemporaneously recruiting women declining randomization may have value as an alternative strategy for comparative effectiveness research.

Objectives—To compare baseline characteristics of randomized participants with nonrandomized participants meeting the same enrollment criteria and to determine whether combining the 2 cohorts in a comprehensive cohort design would be useful for analysis.

Study Design—Premenopausal women with symptomatic uterine fibroids seeking interventional therapy at 3 American academic medical centers were randomized (1:1) in 2 strata based on calculated uterine volume (<700 cc^3 and ≥700 cc^3) to undergo embolization or focused ultrasound surgery. Women who met the same inclusion criteria but declined randomization were offered enrollment in a parallel cohort. Both cohorts were followed up for a maximum of 36 months after treatment. The measures addressed in this report were baseline demographics, symptoms, fibroid and uterine characteristics, and scores on validated quality-of-life measures.

Results—Of 723 women screened, 57 were randomized and 49 underwent treatment (27 with focused ultrasound and 22 with embolization). Seven of the 8 women randomized but not treated were assigned to embolization. Of 34 women in the parallel cohort, 16 elected focused ultrasound and 18 elected embolization. Compared with nonrandomized participants, randomized participants had higher mean body mass index (28.7 vs 25.3 kg/m^2; *P*=.01) and were more likely to be gravid (77% vs 47%; *P*=.003) and smokers (42% vs 12%; *P*=.003). Age, race, uterine volume, number of fibroids, and baseline validated measures of general and disease-specific quality of life, pain, depression, and sexual function did not differ between the groups. When we performed a comprehensive cohort analysis and analyzed by treatment arm, the only baseline difference observed was a higher median McGill Pain Score among women undergoing focused ultrasound (10.5 vs 6; *P*=.03); a similar but nonsignificant trend was seen in Visual Analog Scale scores for pain (median, 39.0 vs 24.0; *P*=.06).

Conclusions—Using a comprehensive cohort analysis of study data could result in additional power and greater generalizability if results are adjusted for baseline differences.

Keywords

focused ultrasound; leiomyomas; study design; uterine artery embolization; uterine fibroids

Introduction

Uterine fibroids (leiomyomas) are a common and burdensome disease of reproductive-aged women, yet quality evidence to inform treatment decisions is currently lacking (1). The few randomized controlled trials (RCTs) comparing fibroid therapies have largely been performed outside the United States (2–10). US-based RCTs studying therapies for the related problem of heavy menstrual bleeding have often experienced recruitment challenges (11–14).

The Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) study is an RCT (NCT00995878, clinicaltrials.gov) funded by the National Institutes of Health to compare 2 minimally invasive therapies approved by the US Food and Drug Administration: uterine artery embolization (UAE) and magnetic resonance imaging (MRI)-guided focused ultrasound surgery (MRgFUS).

Because of slow recruitment for the RCT, women meeting the FIRSTT inclusion criteria who declined randomization were offered enrollment in an abbreviated study protocol. Prior studies have demonstrated that such a comprehensive cohort design (CCD) can be useful because outcomes do not appear to differ when both groups receive the same treatments (15,16). The current report summarizes the baseline data for this trial and tests the hypothesis that contemporaneously recruited women meeting the same enrollment criteria who decline participation can be used in a CCD for fibroid treatment trials. Subsequent reports will use these data to compare safety, efficacy, economics, and ovarian reserve after treatment with UAE or MRgFUS.

Materials and Methods

Overview

The overview of the design of the FIRSTT study has been previously reported (17). Since the initial report, the University of California, San Francisco was added in June 2013 to the initial sites: Mayo Clinic, Rochester, Minnesota, and Duke University, Durham, North Carolina. The institutional review board of each site approved the same study protocol.

Briefly, UAE and MRgFUS were performed according to the clinical standard of care, and treatment costs were designed to be paid by the participant's health insurance. Insurance approval for both procedures was confirmed before randomization. Initially, funding was obtained for a 6-month study (RC1HD063312). Study visits occurred at baseline, day of study treatment, and 6 months after treatment. Telephone follow-up and review of study diaries took place 2, 4, and 6 weeks after treatment.

Protocol modifications are outlined in Supplemental Table 1. Full funding (R01HD060503) allowed for visits at 12, 24, and 36 months after treatment, which included MRI at 24 and 36 months, measurement of ovarian reserve at baseline, 12, 24, and 36 months, and economic analysis of treatments.

Enrollment had been substantially limited because of lack of insurance coverage for MRgFUS, and industry funding was obtained to support treatment if insurance coverage was denied (InSightec, Tirat Carmel, Israel). Thus, women randomized to MRgFUS were allowed to proceed with treatment while insurance appeals took place. This backup payment method was closed at 1 site as of November 1, 2013, and the institution committed to cover these costs. Women in both treatment arms were responsible for copayments and deductibles.

The primary efficacy end point for the 36-month study was additional intervention for symptomatic fibroids during the study period. Change in the symptom severity score (SSS)

subscale of the Uterine Fibroid Symptom and Quality of Life instrument (UFS-QOL) was the key secondary efficacy end point (18). Safety was assessed by examining adverse events. Other specific aims of the study included assessing fibroid regression with MRI, assessing ovarian reserve by examining antimüllerian hormone levels, and conducting an economic analysis of treatment.

Study Population

Full inclusion and exclusion criteria at the study outset have been reported (15). In brief, participants were premenopausal women with symptomatic fibroids and uteri less than 20 gestational weeks in size who were not actively trying for pregnancy. All women underwent MRI with gadolinium contrast during screening. Uterine volume was calculated using the formula for the volume of a prolate ellipsoid, and the number of fibroids with maximal diameter of 3 cm or larger was recorded. Changes in enrollment criteria over time are outlined in Supplemental Table 1. None of the previously treated participants would have been excluded by these protocol changes.

Enrollment and Recruitment

At 2 of the 3 sites, a standard telephone screening instrument was used for prescreening, which sequentially identified exclusion criteria, including perimenopausal or postmenopausal status, women actively seeking pregnancy, prior fibroid interventional therapy, current use of a gonadotropin-releasing hormone analog, and medical contraindications to either study treatment. A study gynecologist subsequently screened each participant to exclude other causes of symptoms and to assess contraindications to either therapy, and MRI results were reviewed by a study radiologist for imaging enrollment criteria.

Multiple modes of recruitment were used and were extended over time (Supplemental Table 1). Two observational cohorts were established in 2011 for women who did not enroll in the RCT. Parallel cohort 1 (PC1) consisted of women who met the RCT enrollment criteria but declined participation. PC1 participants completed all study instruments and underwent assessment of ovarian reserve but did not have follow-up MRIs and received a smaller stipend. Parallel cohort 2 (PC2) included all women undergoing fibroid therapy. The protocol for PC2 involved obtaining limited baseline data, assessing ovarian reserve, and collecting economic costs; participants received a minimal stipend. Two sites participated in PC1, and 1 participated in PC2.

Baseline Measures

Baseline questionnaires were administered at the participant’s initial visit; we attempted to schedule women in the early proliferative phase. The collected validated measures included the UFS-QOL (18), Short Form-36 (RAND Corporation) (19), the Center for Epidemiologic Studies Depression Scale (CES-D) (20), Female Sexual Function Index (FSFI) (21), McGill Pain Score (MPS) (22), and Visual Analog Scale for Pain (VAS). Detailed information on study instruments has been reported previously (17).

Randomization

The randomization scheme was stratified by study site and calculated uterine volume: smaller than 700 cc^3 and 700 cc^3 or larger. The randomization was performed using a web-based application created and supported by the Division of Biomedical Statistics and Informatics at Mayo Clinic, which used a dynamic allocation approach based on the Pocock-Simon method to achieve balance within each stratum (23). After randomization, treatment was typically scheduled within 10 days to minimize the chance of subject loss. Neither participants nor clinical investigators were blinded to study assignment.

Standardized Treatment and Recovery Protocols

UAE and MRgFUS were performed using standardized protocols, and all participants received the same discharge instructions and prescriptions.

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) consisted of the study statistician (A.L.W.), Dr. Bradley Van Voorhis, a nationally recognized gynecologist and fibroid expert at the University of Iowa, and Dr. James Spies, a nationally recognized interventional radiologist at Georgetown University with expertise in UAE. The National Institutes of Health project officer was an ex officio member of the DSMB.

Statistical Considerations

An intention-to-treat analysis was conducted. The initial sample size calculations were conducted to detect differences between the 2 treatment arms for a) the need for additional interventional therapy for symptomatic fibroids over the course of the follow-up period, and b) the mean (SD) reduction (compared with baseline) in UFS-QOL SSS. Without published data on MRgFUS outcomes at 36 months at that time, calculations were based on published outcomes at 24 months: a) 20% and 37.5% of patients needing additional therapy after UAE and MRgFUS, respectively, and b) mean (SD) SSS decreases of 40.1 (25.2) and 28.1 (23.6) from baseline scores for UAE and MRgFUS, respectively (24–26). The study was designed to recruit 99 women per treatment arm, which provided statistical power of 78% and 93%, respectively, to detect the anticipated differences in outcomes a and b. These calculations were based on a 2-sided χ^2 test and t test with a type I error of 0.05. There were no a priori stopping rules.

An interim analysis was conducted by the study statistician in February 2014 to assess the results and to determine whether study enrollment should be terminated early given the slow enrollment. Although too few participants had reached the 36-month point to assess the primary end point, statistically significant differences were observed between treatments for SSS over 24 months. The results were presented by blinded group assignment and reviewed by study investigators and the DSMB. The decision was made to end study enrollment as of August 1, 2014, to allow all participants to have at least 12 months of follow-up within the study. In performing the interim analysis, missed follow-up visits were identified at 1 site, and enrollment was closed at that site on March 18, 2014.

Demographic and baseline characteristics were summarized using standard descriptive statistics: frequency (percentage) for categorical variables and mean (SD) or median (interquartile range [IQR]) for continuous variables. Comparisons between groups (RCT vs PC1 and MRgFUS vs UAE) were evaluated using the χ^2 test or Fisher's exact test for categorical variables and the 2-sample *t* test or Wilcoxon rank sum test for continuous variables. All calculated *P* values were 2-sided, and *P* values less than .05 were considered statistically significant. Analyses were performed using SAS software version 9.3 (SAS Institute, Inc).

Results

Inclusions and Exclusions

Across study sites, 723 women were prescreened and 568 (79%) were excluded. The remaining 155 women consented to study participation and were seen for an initial study visit (Figure). Of these, 57 women (37%) made up the RCT group. Uterine size was less than 700 cc^3 in 41 (72%) of the RCT participants. Among the 57 women, 49 (86%) underwent study treatment: 22 UAE and 27 MRgFUS (Figure). Of the 8 women randomized but not treated, 7 were assigned to the UAE group. A protocol violation occurred in 1 of these 7 participants: she was randomized to UAE but then was subsequently assigned to MRgFUS at a second site before the dual randomization was discovered. None of these 8 participants underwent either study treatment. A majority of the 27 women undergoing MRgFUS had treatment funded either by industry (8; 30%) or institutional (7; 26%) funding.

Thirty-eight women (25%) met all enrollment criteria but declined participation; 34 of these women participated in the PC1 observational cohort: 18 underwent UAE and 16 underwent MRgFUS (Figure). Of the women who had consented, 60 (39%) did not meet the inclusion criteria for the RCT. Having an MRI finding that was an exclusion criterion was the most common reason for exclusion. Thirty-eight of the 60 women excluded were at the site participating in PC2, and 28 (74%) consented to be included in PC2 (Figure).

RCT Cohort

Complete demographic and clinical information for the RCT cohort is shown in Table 1. Women enrolled in the RCT were typical of women with uterine fibroids: mean (SD) age was 44.3 (4.7) years, body mass index was 28.7 (5.5) kg/m^2, and 24% had experienced infertility. The RCT participants also tended to reflect the racial diversity of the United States, except for considerable underrepresentation of Hispanic women (5%). The majority of RCT participants were current alcohol users (82%) and regularly exercised (75%), whereas 18% were current smokers and 42% reported having more than 100 cigarettes in their lifetime.

Median (IQR) uterine size was 563 (402–693) cc^3; 44% had 1 fibroid and 15% had 4 or more fibroids at least 3 cm in greatest diameter (Table 1). Most women had multiple fibroid symptoms. Bulk symptoms were the most common dominant symptom reported (Table 1).

Medical comorbid conditions were relatively common; the most frequent conditions among 55 respondents were ovarian cysts (15%), depression (11%), fibrocystic breast disease (11%), hypertension (11%), endometriosis (9%), and hypothyroidism (9%). Other gynecologic conditions were rare and included adenomyosis (4%), endometrial polyps (2%), and uterine prolapse (2%). Among 56 participants responding, most had some type of prior surgery (79%) and reported taking regular medication (68%), but none had diabetes.

Fibroid Symptoms

Validated measures confirmed that women in the RCT had substantial fibroid symptoms, with a mean UFS-QOL SSS of 53.8 (19.5), and impaired quality of life, with a UFS-QOL total health-related quality of life subscale score of 50.8 (18.8) (Table 1). General health status was also impaired compared with population means, as captured by the Short Form-36 score (Table 1); the most impairment was seen on the energy/fatigue subscore (37.3 [23.7]). Pain as measured by the MPS (median [IQR], 9.0 [4.0–17.0]) and VAS (median [IQR], 35.5 [7.5–60.5]) was consistent with mild pain and was comparable to baseline pain in the previous uterine fibroid study using MPS (27). The CES-D mean score (19.5 [7.2]) suggested mild depression, and the mean FSFI score (19.5 [10.7]) suggested lower sexual function than in the general population.

Parallel Cohorts

Women enrolled in PC1 were very similar to their RCT counterparts (Table 1). They did, however, have a significantly lower mean body mass index (P=.01), were less likely to have had a pregnancy (P=.003), and were less likely to be current (P=.048) or ever-smokers (P=.003) (Table 1). RCT and PC1 participants had no significant differences in fibroid characteristics, self-reported fibroid symptoms, median uterine volumes, or scores on any validated instruments (Table 1).

Women who enrolled in PC2 (Supplemental Table 2) were different from women who met enrollment criteria for the other protocols (Table 1). Compared with RCT and PC1 participants, PC2 participants had larger uteri (median, 670 vs 584 cc^3), were younger at the time of fibroid diagnosis (35.2 [9.3] vs 40.3 [6.9] years), and had a greater proportion of women with 4 or more measured fibroids (30% vs 14%). PC2 participants were also more likely to report infertility (50% vs 23%) but had similar validated measures (Supplemental Table 2, Table 1).

UAE vs MRgFUS

Within each cohort (RCT and PC1), there were few differences between the UAE and MRgFUS arms (Tables 2 and 3). When the 2 cohorts were combined, there were no significant differences in patient or fibroid characteristics between treatment arms (Table 2). However, the median baseline MPS score was significantly higher in the MRgFUS arm (10.5 vs 6.0 [UAE]; P=.03); a similar but nonsignificant trend was seen in VAS scores (median, 39.0 vs 24.0; P=.06) (Table 3). No correlation was seen between smoking and pain scores (data not shown).

Because of the differential loss of participants between randomization and treatment in the RCT, an analysis of treated participants was also performed (Supplemental Tables 3 and 4). Again, no significant differences were found between the MRgFUS and UAE arms in patient or fibroid characteristics (Supplemental Table 3). Although not statistically significant, the same trend was seen in pain scores as in the intention-to-treat analysis, with patients in the MRgFUS arm reporting higher pain scores than patients in the UAE arm on the MPS (median, 10.0 vs 7.0; P=.08) and the VAS (median, 38.0 vs 25.0; P=.10) (Supplemental Table 4).

Comment

Evaluating the comparative effectiveness of interventional therapies for treatment of uterine fibroids is an important area of research, and an RCT provides the highest level of evidence. However, RCTs for interventional fibroid therapies have been difficult to perform in United States populations; the FIRSTT study further demonstrates this challenge. Recruitment for the FIRSTT study also faced the challenge that despite receiving US Food and Drug Administration approval in 2004, many insurers continue to classify MRgFUS as an investigational therapy and deny coverage for treatment. Thus, the conundrum exists that insurers await high-quality evidence of efficacy for new treatments, while RCTs remain difficult to conduct because of lack of insurance coverage.

Our study findings provide evidence that a CCD analysis would be appropriate for FIRSTT trial data. This type of design has been advocated in the past to increase the generalizability of RCT results and has been used in high-profile research studies, including the Women's Health Initiative (15,16,28,29). In our study, the enrollment criteria that defined the RCT and PC1 groups resulted in similar participant characteristics, which suggests that the criteria, rather than the act of randomization, was the key variable. In addition, women not meeting these criteria who enrolled in the PC2 cohort were different in many important ways.

The FIRSTT trial also demonstrates that having financial coverage for treatment in place substantially increases enrollment. The fact that all but 1 of the participants who chose not to undergo treatment were assigned to UAE suggests that women enrolling in the RCT were seeking access to MRgFUS, and the study funding of treatment appears to have been an enticement to enroll. However, given the overall similarity between treatment arms and the higher levels of baseline pain reported in the MRgFUS group, it does not appear that this coverage induced recruitment of women who reported fewer symptoms at baseline. Interestingly, women meeting the same enrollment criteria but deciding to choose their treatment selected UAE and MRgFUS in nearly equal numbers. This suggests that the critical distinction for fibroid studies could be the definition of the population based on enrollment criteria rather than the act of randomization.

Going forward, assessing FIRSTT trial outcomes of only participants undergoing treatment appears to be more appropriate given the substantial number of withdrawals that differentially affected the UAE arm of the RCT. Although the statistical difference in pain scores is attenuated, adjustments for baseline pain scores should be made in future analyses. Other differences between arms also may affect outcomes. For example, women undergoing

UAE were more likely to have only 1 or 2 fibroids of 3 cm or larger; this may be important because MRgFUS targets individual fibroids and UAE is a global uterine therapy (1).

A clear limitation of the study, however, is that important unmeasured confounders may exist among women in the PC1 cohort that differ between arms and may affect outcomes. If there are additional confounders, this effect may be magnified because the sample size is relatively small.

Another key limitation of this study was the failure to meet our enrollment targets. More specifically, our goal had been to recruit more women of African descent given the increased severity of disease in this population and amid evidence that these women have different patterns of disease and prefer uterine-sparing therapies (30,31). Other than this limitation, our cohort did reflect the population of women with symptomatic fibroids and significant impairment of quality of life, which is consistent with other fibroid studies as measured by standardized instruments. Women in the RCT also reflect the US population in terms of smoking status, with an approximate rate of 18% (32).

Our finding that women in the RCT and PC1 groups were similar in several key features, including symptoms, objective measures of fibroid burden, and most baseline validated measures, was reassuring given the broad categories of inclusion. Conducting a CCD study with adjustment for baseline factors may prove to be a useful model for future studies of interventional fibroid therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CCD	comprehensive cohort design
CES-D	Center for Epidemiologic Studies Depression Scale
DSMB	Data Safety Monitoring Board
FIRSTT	Fibroid Interventions: Reducing Symptoms Today and Tomorrow
FSFI	Female Sexual Function Index
IQR	interquartile range
MPS	McGill Pain Score

MRgFUS	magnetic resonance imaging–guided focused ultrasound surgery
MRI	magnetic resonance imaging
PC1	parallel cohort 1
PC2	parallel cohort 2
RCT	randomized controlled trial
SSS	symptom severity score
UAE	uterine artery embolization
UFS-QOL	Uterine Fibroid Symptom and Quality of Life instrument
VAS	Visual Analog Scale for Pain

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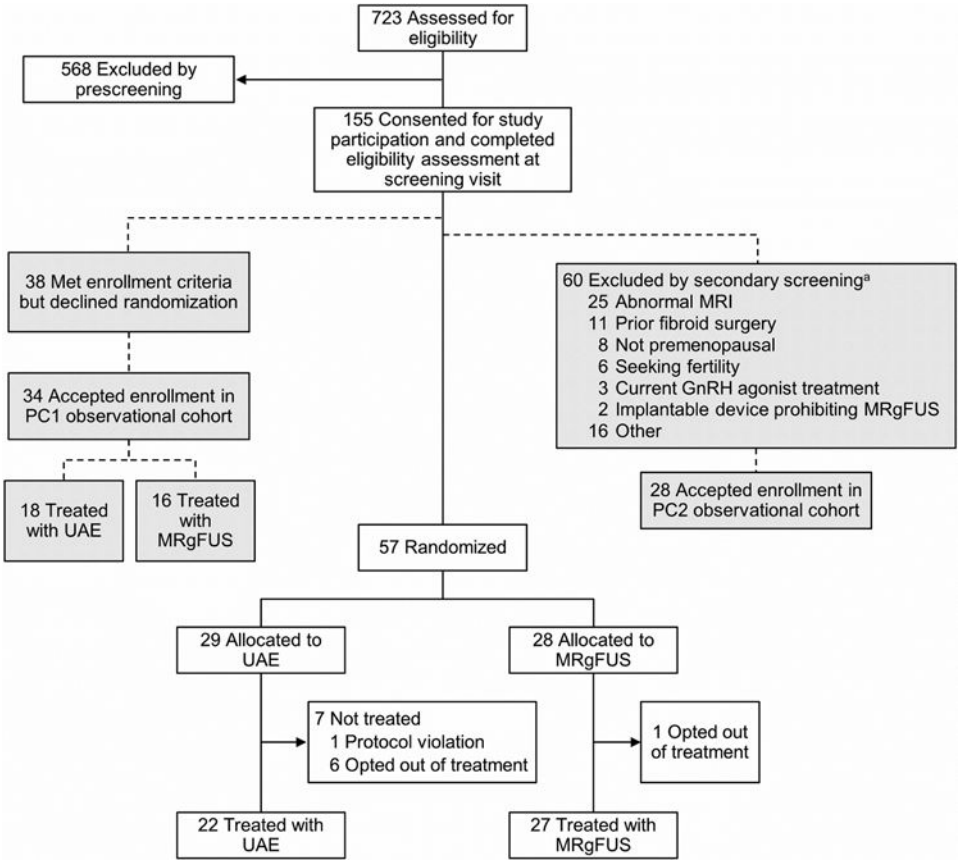

Figure.

CONSORT Flow Diagram. Solid lines and white boxes show disposition of randomized controlled trial participants. Dashed lines and shaded boxes indicate the flow of participants who entered either PC1 or PC2. GnRH indicates gonadotropin-releasing hormone; MRgFUS, magnetic resonance imaging–guided focused ultrasound surgery; MRI, magnetic resonance imaging; PC1, parallel cohort 1; PC2, parallel cohort 2; UAE, uterine artery embolization. [a]Eleven patients had 2 exclusion criteria.

Table 1

Baseline Characteristics and Validated Measures for the Study Cohorts[a]

Characteristic or Measure	Overall (N=91)	Study Cohort		P[b]
		RCT (n=57)	PC1 (n=34)	
Patient characteristics				
Age at treatment, y[c]	44.5 (5.0)	44.3 (4.7)	44.9 (5.4)	.60
Race				.15
African American	11 (12)	9 (16)	2 (6)	
Asian	5 (5)	1 (2)	4 (12)	
Hispanic or Latina	5 (5)	3 (5)	2 (6)	
White	65 (71)	42 (74)	23 (68)	
Other	5 (5)	2 (4)	3 (9)	
BMI, kg/m^2	27.4 (5.9)	28.7 (5.5)	25.3 (6.0)	.01
BMI category				.01
Underweight	1 (1)	0 (0)	1 (3)	
Normal	29 (32)	14 (25)	15 (44)	
Overweight	34 (37)	22 (39)	12 (35)	
Obese	27 (30)	21 (37)	6 (18)	
Gravidity				.003
0	31 (34)	13 (23)	18 (53)	
≥1	60 (66)	44 (77)	16 (47)	
Parity				.12
0	44 (48)	24 (42)	20 (59)	
≥1	47 (52)	33 (58)	14 (41)	
History of infertility	20 (23) (n=88)	13 (24) (n=55)	7 (21) (n=33)	.79
Education	(n=88)	(n=56)	(n=32)	.17
Some high school	1 (1)	1 (2)	0 (0)	
High school graduate	6 (7)	4 (7)	2 (6)	
Some college	16 (18)	11 (20)	5 (16)	
College graduate with 4-year degree	25 (28)	18 (32)	7 (22)	
Postgraduate education	40 (45)	22 (39)	18 (56)	
Smoked >100 cigarettes in lifetime	28 (31) (n=90)	24 (42)	4 (12) (n=33)	.003
Current smoker	11 (12)	10 (18)	1 (3)	.048
Current alcohol use	71 (80) (n=89)	46 (82) (n=56)	25 (76) (n=33)	.47
Regular exercise	65 (73) (n=89)	42 (75) (n=56)	23 (70) (n=33)	.59
Insurance status				.56
Commercial	83 (91)	53 (93)	30 (88)	
Government	3 (3)	1 (2)	2 (6)	
Self-pay	5 (5)	3 (5)	2 (6)	

Characteristic or Measure	Overall (N=91)	Study Cohort		P[b]
		RCT (n=57)	PC1 (n=34)	
Uterine and fibroid characteristics				
Uterine volume, cc[3]	584 (395–756)	563 (402–693)	594 (368–814)	.82
Number of fibroids ≥3 cm				.36
0	3 (3)	0 (0)	3 (5)	
1	44 (48)	15 (44)	29 (51)	
2	17 (19)	9 (27)	8 (14)	
3	14 (15)	5 (15)	9 (16)	
≥4	13 (14)	5 (15)	8 (14)	
Age at fibroid diagnosis, y	40.3 (6.9)	39.5 (7.1)	41.7 (6.4)	.16
Self-reported fibroid-related symptoms				
Presenting symptom(s)	(n=89)		(n=32)	
Bulk symptoms	85 (96)	55 (97)	30 (94)	.62
Heavy menstrual bleeding	73 (82)	48 (84)	25 (78)	.47
Pain or fatigue	78 (88)	51 (90)	27 (84)	.52
Predominant symptom	(n=89)		(n=32)	.21
Bulk symptoms	32 (36)	22 (39)	10 (31)	
Heavy menstrual bleeding	30 (34)	15 (26)	15 (47)	
Pain or fatigue	16 (18)	11 (19)	5 (16)	
>1 symptom	11 (12)	9 (16)	2 (6)	
Baseline validated measures				
UFS-QOL				
Symptom severity score	53.5 (19.5)	53.8 (19.5)	53.1 (19.9)	.89
Health-related quality of life	51.6 (20.3)	50.8 (18.8)	52.8 (22.9)	.67
Short Form-36				
Mental composite score	42.9 (10.6)	41.7 (10.7)	45.0 (10.4)	.16
Physical composite score	45.1 (9.2)	44.8 (9.1)	45.7 (9.6)	.69
MPS total pain score	8.0 (3.0–15.0)	9.0 (4.0–17.0)	7.5 (2.0–12.0)	.17
VAS, intensity score	28.0 (5.0–59.0)	35.5 (7.5–60.5)	23.0 (4.0–49.0)	.11
CES-D				
Total score	19.0 (6.8)	19.5 (7.2)	18.1 (6.3)	.38
Met criteria for subthreshold depression symptoms[d]	55 (66) (n=84)	37 (71) (n=52)	18 (56) (n=32)	.16
FSFI, full scale score	19.8 (10.2)	19.5 (10.7)	20.1 (9.3)	.81

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; FSFI, Female Sexual Function Index; MPS, McGill Pain Score; PC1, parallel cohort 1; RCT, randomized controlled trial; UFS-QOL, Uterine Fibroid Symptom and Quality of Life scale; VAS, Visual Analog Scale for Pain.

[a]Values are mean (SD), median (interquartile range), or No. of patients (%).

[b]For the clinical characteristics, comparisons between groups were evaluated using the χ^2 test or Fisher exact test for categorical variables, the 2-sample *t* test for age and BMI, and the Wilcoxon rank sum test for uterine volume. For the validated measures, comparisons between groups were evaluated using the Wilcoxon rank sum test for the pain scales since the distributions were positively skewed, the 2-sample *t* test for all other continuous measures, and the χ^2 test for the proportion meeting criteria for subthreshold depression symptoms.

[c] Age at treatment was imputed for the 8 participants who were randomized and not treated by using the date the baseline questionnaire was completed.

[d] A CES-D score of 16 or higher meets the criteria for having subthreshold depression symptoms.

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Table 2

Characteristics of the Study Cohorts by Treatment (Intention to Treat)[a]

Characteristic	RCT		PC1		Overall		
	MRgFUS (n=28)	UAE (n=29)	MRgFUS (n=16)	UAE (n=18)	MRgFUS (n=44)	UAE (n=47)	*P*[b]
Patient characteristics							
Age at treatment, y[c]	44.3 (4.5)	44.4 (5.0)	44.1 (6.2)	45.6 (4.7)	44.2 (5.1)	44.9 (4.9)	.52
Race							.28
African American	4 (14)	5 (17)	2 (13)	0 (0)	6 (14)	5 (11)	
Asian	1 (4)	0 (0)	3 (19)	1 (6)	4 (9)	1 (2)	
Hispanic or Latina	3 (11)	0 (0)	1 (6)	1 (6)	4 (9)	1 (2)	
White	18 (64)	24 (83)	10 (63)	13 (72)	28 (64)	37 (79)	
Other	2 (7)	0 (0)	0 (0)	3 (17)	2 (5)	3 (6)	
BMI, kg/m^2	27.7 (5.8)	29.6 (5.0)	25.6 (5.2)	25.0 (6.8)	26.9 (6)	27.9 (6.1)	.46
BMI category							.39
Underweight	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	1 (2)	
Normal	9 (32)	5 (17)	8 (50)	7 (39)	17 (39)	12 (26)	
Overweight	9 (32)	13 (45)	6 (38)	6 (33)	15 (34)	19 (40)	
Obese	10 (36)	11 (38)	2 (13)	4 (22)	12 (27)	15 (32)	
Gravidity							.66
0	7 (25)	6 (21)	9 (56)	9 (50)	16 (36)	15 (32)	
≥1	21 (75)	23 (79)	7 (44)	9 (50)	28 (64)	32 (68)	
Parity							.47
0	13 (46)	11 (38)	10 (63)	10 (56)	23 (52)	21 (45)	
≥1	15 (54)	18 (62)	6 (38)	8 (44)	21 (48)	26 (55)	
History of infertility	4 (15) (n=27)	9 (32) (n=28)	4 (25)	3 (18) (n=17)	8 (19) (n=43)	12 (27) (n=45)	.37
Education		(n=28)	(n=15)	(n=17)	(n=43)	(n=45)	.86
Some high school	1 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	
High school graduate	2 (7)	2 (7)	2 (13)	0 (0)	4 (9)	2 (4)	
Some college	5 (18)	6 (21)	2 (13)	3 (18)	7 (16)	9 (20)	
College graduate with 4-year degree	8 (29)	10 (36)	3 (20)	4 (24)	11 (26)	14 (31)	

Characteristic	RCT MRgFUS (n=28)	RCT UAE (n=29)	PC1 MRgFUS (n=16)	PC1 UAE (n=18)	Overall MRgFUS (n=44)	Overall UAE (n=47)	P[b]
Postgraduate education	12 (43)	10 (36)	8 (53)	10 (59)	20 (47)	20 (44)	
Smoked >100 cigarettes in lifetime	15 (54)	9 (31)	1 (6)	3 (18)	16 (36)	12 (26) (n=46)	.29
Current smoker	6 (21)	4 (14)	0 (0)	1 (6)	6 (14)	5 (11)	.66
Current alcohol use	23 (82)	23/28 (82) (n=28)	12 (75)	13 (77) (n=17)	35 (80)	36 (80) (n=45)	.96
Regular exercise	20 (71)	22/28 (79) (n=28)	9 (56)	14 (82) (n=17)	29 (66)	36 (80) (n=45)	.13
Insurance status							.80
Commercial	26 (93)	27 (93)	15 (94)	15 (83)	41 (93)	42 (89)	
Government	1 (4)	0 (0)	0 (0)	2 (11)	1 (2)	2 (4)	
Self-pay	1 (4)	2 (7)	1 (6)	1 (6)	2 (5)	3 (6)	
Uterine and fibroid characteristics							
Uterine volume, cc^3	567 (369–701)	563 (402–690)	613 (437–732)	533 (338–922)	586 (400–708)	563 (395–860)	.96
Number of fibroids ≥3 cm							.12
0	2 (7)	1 (3)	0 (0)	0 (0)	2 (5)	1 (2)	
1	11 (39)	18 (62)	7 (44)	8 (44)	18 (41)	26 (55)	
2	2 (7)	6 (21)	3 (19)	6 (33)	5 (11)	12 (26)	
3	8 (29)	1 (3)	3 (19)	2 (11)	11 (25)	3 (6)	
≥4	5 (18)	3 (10)	3 (19)	2 (11)	8 (18)	5 (11)	
Age at fibroid diagnosis, y	39.6 (7.1)	39.3 (7.3)	40.3 (7.2)	42.8 (5.6)	39.9 (7.0)	40.6 (6.9)	.61
Self-reported fibroid-related symptoms							
Presenting symptom(s)				(n=16)		(n=45)	
Bulk symptoms	28 (100)	27 (93)	16 (100)	14 (88)	44 (100)	41 (91)	.12
Heavy menstrual bleeding	25 (89)	23 (79)	12 (75)	13 (81)	37 (84)	36 (80)	.62
Pain or fatigue	26 (93)	25 (86)	14 (88)	13 (81)	40 (91)	38 (84)	.35
Predominant symptom				(n=16)			.14
Bulk symptoms	14 (50)	8 (28)	5 (31)	5 (31)	19 (43)	13 (29)	
Heavy menstrual bleeding	3 (11)	12 (41)	7 (44)	8 (50)	10 (23)	20 (44)	
Pain or fatigue	6 (21)	5 (17)	4 (25)	1 (6)	10 (23)	6 (13)	
>1 Symptom	5 (18)	4 (14)	0 (0)	2 (13)	5 (11)	6 (13)	

Abbreviations: BMI, body mass index; MRgFUS, magnetic resonance imaging–guided focused ultrasound surgery; PC1, parallel cohort 1; RCT, randomized controlled trial; UAE, uterine artery embolization.

[a] Values are mean (SD), median (interquartile range), or No. of patients (%).

[b] Comparisons between the 2 overall treatment arms were evaluated using the χ^2 test or Fisher exact test for categorical variables, the 2-sample *t* test for age and BMI, and the Wilcoxon rank sum test for uterine volume.

[c] Age at treatment was imputed for the 8 participants who were randomized and not treated by using the date the baseline questionnaire was completed.

Table 3

Baseline Validated Measures by Treatment (Intention to Treat)[a]

	RCT		PC1		Overall		
Validated Questionnaire	**MRgFUS (n=28)**	**UAE (n=29)**	**MRgFUS (n=16)**	**UAE (n=18)**	**MRgFUS (n=44)**	**UAE (n=47)**	***P*[b]**
UFS-QOL							
Symptom severity score	54.6 (21.2)	52.9 (18.1)	52.9 (17.0)	53.3 (22.9)	54.0 (19.6)	53.1 (19.7)	.82
Health-related quality of life	49.5 (19.7)	52.2 (18.1)	55.4 (17.3)	50.2 (27.7)	51.7 (18.8)	51.4 (22.1)	.94
Short Form-36							
Mental composite score	39.8 (9.3)	43.8 (11.9)	43.4 (11.1)	46.6 (9.8)	41.1 (10.0)	44.9 (11.1)	.10
Physical composite score	43.0 (8.9)	46.8 (9.1)	45.1 (9.2)	46.2 (10.3)	43.8 (9.0)	46.6 (9.4)	.16
MPS total pain score	11 (6.0–18.5)	7.0 (3.0–13.0)	9.5 (3.5–13.5)	5.0 (2.0–9.0)	10.5 (6.0–17.0)	6 (2.0–11.0)	.03
VAS, intensity score	47.0 (27.5–70.0)	26.0 (3.5–54.0)	24 (4.0–49.0)	15.0 (4.0–60.0)	39.0 (21.5–64.5)	24.0 (4.0–56.0)	.06
CES-D							
Total score	20.9 (7.0)	18.0 (7.1)	17.9 (6.5)	18.3 (6.3)	19.8 (6.9)	18.1 (6.7)	.26
Met criteria for subthreshold depression symptoms[c]	22/27 (81)	15/25 (60)	8 (50)	10/16 (63)	30/43 (70)	25/41 (61)	.40
FSFI, full scale score	20.2 (10.8)	19.0 (10.9)	18.8 (10.3)	21.3 (8.5)	19.7 (10.5)	19.8 (10.0)	.95

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; FSFI, Female Sexual Function Index; MPS, McGill Pain Score; PC1, parallel cohort 1; RCT, randomized controlled trial; UFS-QOL, Uterine Fibroid Symptom and Quality of Life scale; VAS, Visual Analog Scale for Pain.

[a] Values are mean (SD), median (interquartile range), or No. of patients (%).

[b] Comparisons between groups were evaluated using the Wilcoxon rank sum tests for the pain scales since the distributions were positively skewed, the 2-sample *t* test for all other continuous measures, and the χ^2 test for the proportion meeting criteria for subthreshold depression symptoms.

[c] A CES-D score of at least 16 meets the criteria for having subthreshold depression symptoms.