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Recruitment and Retention of Women for Clinical Leiomyoma Trials

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Abstract

Background—Subject recruitment and retention in clinical leiomyoma trials is challenging. We evaluated strategies to increase patient enrollment and completion in leiomyoma trials.

Materials and methods—Randomized trials for treatment of symptomatic leiomyoma published from 2000 through 2008 were evaluated and thirteen trials were selected. Subject enrollment and completion rates, recruitment methods and reasons for patient drop-out were assessed.

Results—Recruitment by study personnel or clinic staff during evaluation for symptomatic leiomyoma was the most common strategy for enrollment. Additional methods included local media, internet postings and physician referrals. Seven to 85% of patients enrolled after screening, with a median enrollment of 70%. Sixty-five to 100% of patients completed the study after enrollment with a median completion rate of 89%. Reasons for drop-out at the screening stage included failure to meet inclusion criteria, patient refusal and patient preference for specific treatment. Commonly reported reasons for drop-out after enrollment were refusal of treatment following randomization, adverse reaction to study intervention and non-compliance with study protocol or follow-up visits.

Conclusion—Women with symptomatic uterine leiomyomas may be attracted to participate in leiomyoma trials, however desire for specific treatment and persistent symptoms following intervention may hinder their participation. Randomization to placebo treatment and stringent inclusion criteria appear to adversely impact accrual. A wide range of recruiting tactics is needed and media sources or direct mailings may prove particularly effective to improve subject recruitment and retention in clinical leiomyoma trials.

Keywords

Leiomyoma; Clinical trials; Recruitment; Retention

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Introduction

In the United States, uterine leiomyomas are the most common gynecologic tumor in reproductive-aged women affecting as many as 70% of women by age 50 (1). Black women are disproportionately affected by uterine leiomyomas compared to other ethnic and racial groups (2–4). Up to 50% of women with leiomyomata have symptoms of pelvic pain, menstrual irregularities and/or infertility that prompt intervention (1,5). The treatment for leiomyomas is usually surgical removal of the entire uterus (hysterectomy) or removal of the leiomyomas only (myomectomy). Non-surgical options include medical therapy with hormone-suppressing agents and radiologic procedures to occlude uterine blood supply (uterine artery embolization: UAE) or reduce leiomyomas with targeted ultrasound treatment. Though hysterectomy is curative, leiomyomas and their associated symptoms often recur after other treatments.

Total direct cost to the U.S. health care system for the management of uterine leiomyomas is estimated at $2.1 billion per year (6). Because the clinical and financial burdens of this disease are large, new treatment strategies would be welcome. Several clinical trials have evaluated the effectiveness of various surgical and non-surgical treatments. However, subject enrollment and continuance are challenging, and completion rates are often low.

Many barriers to recruitment and retention in clinical trials exist and it is important to understand how these barriers impact patient participation and the generalizability of reported results. The literature from oncology trials identifies various patient factors such as lack of awareness of ongoing trials, fear or distrust of the medical establishment and concerns over loss of insurance benefits due to participation in “experimental” therapy as causes for low participation (7–9). This may be particularly important within black communities, where a lower level of trust has been reported as a significant barrier to participation (10,11). At the healthcare provider level, lack of awareness of ongoing trials, belief that standard therapy is best and concern over loss of control of the patient’s care may also lead to lower participation rates (9). Though these barriers are cited in the context of cancer research clinical trials, they are applicable to other areas of investigation as well. To address low patient participation in clinical trials, more clinical investigators are devising strategies to overcome these obstacles in order to reach recruitment goals.

Though enrollment and completion rates for cancer trials have been evaluated, no reports have examined these measures in leiomyoma clinical trials. Identification of the obstacles to study enrollment and completion may allow us to tailor future recruitment strategies to our target population of women, especially black women, who are disproportionately affected by this condition and who have had low participation rates. To identify such obstacles, we examined enrollment and retention rates and recruitment strategies in published randomized leiomyoma treatment trials.

Methods

Clinical leiomyoma studies published from 2000 through 2008 were identified using the PubMed, Scopus and EMBASE search engines and the key words leiomyoma, fibroid and clinical trial. Only randomized controlled trials were selected, as many of these investigations were reported according to CONSORT guidelines and therefore included more complete information on patient flow through the study (12). Information on the number of patients screened, enrolled and completing each trial was collected. We also collected data on recruitment methods and reasons for patient withdrawal from the studies. Investigators were contacted regarding unpublished data, and additional information they provided was included. We evaluated the reporting of patient demographics, specifically ethnicity, among studies

selected. All information was obtained from the published manuscripts or through correspondence with the original authors.

Results

The initial search identified 269 abstracts of original articles related to leiomyoma clinical trials and 13 studies met inclusion criteria (13–25). The studies' duration ranged from three to twenty-four months. The ethnicity of study participants was reported in eleven of the thirteen studies. Black women comprised over 50% of the study population in one-third of the studies identified. The percentage of black participants ranged from <1–72% in these studies.

Four of the thirteen trials provided no information on recruitment strategies. Among the studies providing this information, recruitment by study personnel or clinic staff was employed. Nurses or physicians involved with the study informed patients about the trial during a scheduled visit for evaluation of symptomatic leiomyoma or upon referral from an outside physician. Interested patients were then screened to assess their eligibility for study enrollment.

Three studies reported other recruitment methods in addition to study personnel, with variable overall enrollment rates (7–51%). Additional methods included recruitment through local media, referrals from community physicians, and internet postings (Table 2). In one study, the most successful recruitment methods were television and radio advertisements, word of mouth, and internet sites that described the study. Television public service announcements (PSA) accounted for 25.5% of the referrals while radio, word of mouth and the internet accounted for 18.6%, 17% and 16% respectively. Physician referrals, community outreach through health fairs and collaboration with local churches, recruitment by non-physician providers and newspaper advertisements were individually responsible for less than 10% of the referrals (15, unpublished data). Although the recruitment strategies of television and radio advertisements were the most successful, they were also the most expensive. Due to reporting of additional recruitment strategies in only a few studies and wide variation in enrollment rates, it is difficult to make comparisons regarding the effectiveness of various methods.

Most patient drop-out occurred at the screening stage. Information on the number of women screened was available for 9 of the 13 studies; a total of 2,180 patients were initially screened and 971 (45%) enrolled. The range of patients enrolled after screening was broad (7–85%) with a median enrollment of 70. Three trials reported enrollment >80%; two of these trials included surgical intervention. In the four remaining studies, 361 patients enrolled.

The most frequently cited causes of drop-out during screening were patient refusal to participate after learning about the study, failure to meet inclusion criteria and patient desire for specific treatment.

Though recruitment costs can influence strategies for enrollment and retention, this information was only available for one of the identified trials (15, unpublished data). Additionally, the clinical investigation by Levens et al. was the only one to report monetary remuneration of study participants (unpublished data).

All thirteen trials provided information regarding follow-up and reasons for withdrawal once patients were enrolled. The median completion rate for enrolled subjects was 89% with a range of 65–100%. Thus, of the patients who enrolled for investigation, study completion was high; however, completion rates for all patients screened were low. Three trials reported <10% of completers per patient screened and two of these trials included a placebo arm (Table 1). Common causes for patient withdrawal once the study was underway were adverse effects from the study intervention, participant non-compliance, withdrawal of consent and failure to follow-up (Table 2). Information on retention strategies was not published.

Discussion

Recruitment of patients for clinical leiomyoma trials is very challenging. This review identified some obstacles affecting enrollment and completion rates. We evaluated thirteen studies that provided information on recruitment and retention strategies and success. The greatest drop out of patients occurred between screening and enrollment and reduced the number of patient completers per trial. Of the five trials reporting enrollment rates >70%, only one included a placebo arm whereas 3 of the 4 studies reporting <51% enrollment included placebo allocation. Three of the placebo controlled studies offered surgical treatment at the end of the trial and one offered open-label extension of study drug to participants. Though focus on initial recruitment efforts is important, the impact of study design on patient enrollment rates should not be ignored.

We limited our review to published randomized controlled trials (RCT) that provided a comprehensive description of subject enrollment and progression through each trial. Our findings may be biased by the exclusion of non-randomized studies and those involving short term follow-up of surgical interventions. Issues related to study design, such as randomization to a specific intervention or placebo treatment are likely to impact a subject's willingness to enroll or complete the study. Also, differences in study populations of surgical vs. medical intervention trials may result in varied enrollment and completion rates. Lastly, a publication bias may exist among studies included in our review, the success of recruitment may influence whether these data are included in a manuscript.

Many of these trial reports cited inclusion/exclusion criteria as a cause for patient drop-out before enrollment. Criteria were varied and included premenopausal status, degree of symptoms, size of leiomyomas or uterine volume, indication for surgical intervention and avoidance of hormonal treatment for 3–6 months prior to entering the trial. Trials adopting specific cutoffs for laboratory values (e.g. FSH or hemoglobin) or body mass index (BMI) may have excluded more patients during screening.

Dissatisfaction with treatment allocation following randomization also was cited as a reason for patient drop-out. We believe the possibility of receiving placebo medication instead of active study drug also may have negatively impacted accrual in the placebo controlled investigations, particularly in studies where cross-over to active study medication or surgery was not offered. Patients may find uncertainty regarding treatment allocation and treatment effects to be unacceptable and may decline to participate on this basis alone (26,27). This is consistent with findings from a review of published randomized controlled trials showing that patient preference for a particular treatment was a common reason for non-participation. Some of these preferences included desire not to change medication, desire not to take placebo or request for a specific intervention (28).

It is not surprising that the highest study completion rates occurred in leiomyoma trials involving surgical treatment of all subjects. We assume that a desire for definitive surgical treatment was a strong motivator for patients to remain in these studies until completion. However, when the patient's desired treatment is not an option, we must employ other strategies to encourage their participation. Ensuring that potential subjects receive adequate information regarding the rationale for the study, available treatment options and explanation of the randomization process may increase accrual, although this has not been tested. An alternate strategy may be to offer the study intervention to participants in the placebo arm once they have completed the study.

Successful recruitment requires the use of varied strategies. The experience of Levens et al. suggests that television, radio, word of mouth and the internet are the most successful but most costly methods. In an economically disadvantaged population the internet is unlikely to be an

effective tool. By contrast, more than 95% of households in the U.S. have a television set, giving this vehicle a higher likelihood of success. In a campaign to recruit black participants into a smoking cessation trial, Webb and colleagues found that television, radio and newspaper ads were the most effective recruitment tools (29). Several investigators have reported that direct mailings in the form of flyers or personalized letters were the most economical and effective recruitment strategies in their respective trials (30–32).

In general, the retention of subjects in leiomyoma trials was better than the enrollment rate. However, drop-out still occurred after enrollment, which highlights the need to focus on retention once the study is underway. Developing trusting relationships between study personnel and subjects, provision of incentives and rigorous follow-up efforts have all been described to increase retention (33,34).

The success of recruitment strategies also may depend on the study population. Several reports indicate that minority groups, blacks in particular, participate less often in clinical trials (35, 36). Reasons often cited for low participation are mistrust of the medical establishment stemming from prior unethical research conduct, cultural objections to medical interventions and limited access to ongoing trials. However, several recent studies have found little difference in black subjects' willingness to participate in clinical research; suggesting that access and awareness of ongoing trials are more important factors in this group's participation (37,38). Of the studies reported here, 85% included subject ethnicity in their demographics and black women were under-represented in most of the trials we reviewed. Due to the broad range of black study subjects in the trials reviewed, we are unable to draw conclusions between ethnicity of subjects and participation rates. Future published trials should include this information to establish if a relationship exists.

The goal of future leiomyoma trials is to evaluate the effectiveness of new treatments across the spectrum of women affected by symptomatic uterine leiomyomas. As evidenced by clinical trials in other areas, media sources (television, radio and newspaper) and mailings can be highly effective recruitment tools. Though some recruitment strategies prove more successful than others, a broad range of recruitment strategies is needed if higher enrollment numbers are to be achieved. Potential study subjects should be targeted with culturally adapted radio, television and newspaper advertisements inviting them to participate in ongoing trials. Active outreach efforts by research personnel including continued patient contact and follow-up are critical to achieve higher retention rates. Additionally, elimination of exclusion variables and inclusion of an active treatment in placebo-controlled trials may allow and encourage additional inclusion. Future research in recruitment and retention methods is needed to identify other strategies for improving patient participation in clinical leiomyoma trials.

Abbreviations

UAE	uterine artery embolization

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Table 1

Characteristics of included randomized controlled trials.

Author	Study Intervention	# Screened	# Subjects enrolled (% of screened)	# Completing study (% of screened)	# Completing study (% of enrolled)	Study Duration (months)	Black subjects enrolled (%)
Carbonell et al. (2008)[13]	Mifepristone 5mg vs. 10 mg	123	100 (81)	99 (80)	99 (99)	3	57
Hehenkamp et al. (2008)[14]	UAE* vs. hysterectomy	349	177 (51)	154 (44)	154 (87)	24	25
Levens et al. (2008)[15]	CDB-2914 vs. placebo¶	312	22 (7)	18 (6)	18 (82)	3	72
Mara et al. (2008)[16]	UAE* vs. myomectomy	149	121 (81)	118 (8)	118 (98)	12	<1
Wilkens et al. (2008)[17]	Asoprisnil vs. placebo¶	46	33 (72)	33 (72)	33 (100)	3	12
Chwalisz et al (2007)[18]	Asoprisnil vs. placebo¶¶	**	129 (**)	115 (**)	115 (89)	3	19
Hald et al. (2007)[19]	Laparoscopic occlusion vs. UAE*	**	66 (**)	56 (**)	56 (85)	6	**
Muneyyirci et al. (2007)[20]	Pre-op Goserelin vs. Iron monotherapy¶	**	110 (**)	72 (**)	72 (65)	9	69
Fiscella et al. (2006)[21]	Mifepristone vs. placebo	434	42 (10)	37 (9)	37 (88)	6	52
Mara et al. (2006)[22]	UAE* vs. myomectomy	74	63 (85)	63 (85)	63 (100)	6	<1
Donnez et al (2003)[23]	Fulvestrant vs. goserelin vs. placebo¶	450	313 (70)	301 (67)	301 (96)	3	**
Palomba et al. (2002)[24]	Leuprolide plus raloxifene vs. leuprolide plus placebo	243	100 (41)	91 (37)	91 (91)	6	2
Verspyck et al. (2000)[25]	Leuprorelin vs. lynestrenol¶	**	56 (**)	46 (**)	46 (82)	4	<10

*UAE: uterine artery embolization

** Information not provided

¶ hysterectomy or myomectomy at end of study

¶¶ open label extension of study drug at end of trial

Table 2

Recruitment methods and reasons for study withdrawal.

Author	Study intervention	Recruitment methods	Reasons for withdrawal
Carbonell et al. (2008)[13]	Mifepristone 5mg vs. 10 mg	Study/clinic personnel	Adverse event
Hehenkamp et al. (2008)[14]	UAE* vs. hysterectomy	Study/clinic personnel, local newspaper	Patient preferred treatment, declined allocated treatment
Levens et al. (2008)[15]	CDB-2914 vs. placebo	Study/clinic personnel, media sources, internet postings, community outreach	Declined allocated treatment, pelvic pain, failure to follow-up
Mara et al. (2008)[16]	UAE* vs. myomectomy	Study/clinic personnel	Patient refused enrollment, exclusion criteria, failure to follow-up
Wilkens et al. (2008)[17]	Asoprisnil vs. placebo	Study/clinic personnel	Exclusion criteria
Chwalisz et al (2007)[18]	Asoprisnil vs. placebo	**	Adverse event, protocol violation, withdrawal of consent, failure to follow-up
Hald et al. (2007)[19]	Laparoscopic occlusion vs. UAE*	Study/clinic personnel	Patient preferred treatment, declined allocated treatment, failure to follow-up
Muneyyirci et al. (2007)[20]	Pre-op Goserelin vs. Iron monotherapy	**	Adverse reaction to medication, subject non-compliance, withdrawal of consent, failure to follow-up
Fiscella et al. (2006)[21]	Mifepristone vs. placebo	Study/clinic personnel, local media, community physician referrals	Patient declined following randomization
Mara et al. (2006)[22]	UAE* vs. myomectomy	Study/clinic personnel	Patients declined enrollment
Donnez et al (2003)[23]	Fulvestrant vs. goserelin	Study/clinic personnel	Protocol deviation, adverse event
Palomba et al. (2002)[24]	Leuprolide plus raloxifene vs. leuprolide plus placebo	Study/clinic personnel	Patient non-compliance, failure to follow-up
Verspyck et al. (2000)[25]	Leuprorelin vs. lynestrenol	**	Adverse event, failure to follow-up, protocol deviation

* UAE: uterine artery embolization

** Information not provided