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Challenges in designing a pragmatic clinical trial: the mixed incontinence – medical or surgical approach (MIMOSA) trial experience

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Abstract

Background—Mixed urinary incontinence (MUI) is a common, bothersome condition in women. In MUI, the two subtypes of urinary incontinence that coexist are treated differently; stress urinary incontinence (SUI) is primarily treated surgically while urge urinary incontinence (UUI) is primarily treated medically. There is no evidence to guide the treatment for women with significant bother from both incontinence subtypes. Therefore, investigators of the Urinary Incontinence Treatment Network (UITN) designed and initiated a randomized clinical trial comparing outcomes for two distinct initial treatment approaches for women with mixed urinary incontinence (MUI): therapy initiated with surgery versus therapy initiated with nonsurgical treatment.

Purpose—The aim of this manuscript is to describe the challenges in planning and implementing this randomized clinical trial.

Methods—The mixed incontinence: medical or surgical approach (MIMOSA) trial was designed as a practical or pragmatic clinical trial to establish the relative efficacy of two specific treatment approaches. The design presented many challenging decisions including: (1) selection of practical paradigm; (2) refining inclusion/ exclusion criteria to offer equipoise; (3) selection of feasibility sample size; (4) recruitment challenges for two divergent treatment approaches (medical vs. surgical), and (5) resolution of ethical and methodological issues.

Results—MIMOSA recruitment was planned in two phases, starting with a 5-month pilot and feasibility phase followed by a full trial contingent on the outcome of the first phase. The feasibility portion of the MIMOSA trial started in November 2008. 1198 subjects were screened and approached for study enrollment, but only 27 consented to randomization. The feasibility study was halted due to lack of enrollment in March 2009.

Limitations—The challenges of this trial included a lack of information from subjects who did not enroll, increasing the difficulty of interpreting the feasibility phase.

Conclusions—Successful recruitment to a randomized trial that compares significantly different treatment approaches poses a challenge.

Introduction

This report describes the challenges in designing and implementing the first randomized, multi-center clinical trial to compare medical versus surgical treatment approaches in women with mixed urinary incontinence (MUI). The mixed incontinence: medical or surgical approach (MIMOSA) trial was conducted by investigators of the Urinary Incontinence Treatment Network (UITN), an experienced clinical trials network of the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The UITN is composed of nine clinical sites led by urogynecology and urology principal investigators and a data-coordinating center. The network has successfully completed two randomized surgical trials for stress urinary incontinence, and one nonsurgical trial for urge urinary incontinence.

Background and rationale for the study

Urinary incontinence is a common and costly condition that affects 15–50% of women of all ages and significantly impairs quality of life [1–3]. In neurologically intact women, the two major subtypes of urinary incontinence are urge urinary incontinence (UUI) and stress urinary incontinence (SUI). Stress urinary incontinence usually occurs with physical activity such as exercise, lifting, or sneezing and is generally considered to be a disorder of the urethral sphincter. Urge urinary incontinence is leakage associated with an urge to void which cannot be suppressed and is thought to be caused by involuntary detrusor (bladder) contractions. The treatment for stress urinary incontinence is often surgical while the treatment for urge incontinence is typically medication and/or behavioral therapy.

These two incontinence subtypes commonly coexist in a condition referred to as MUI. MUI can be defined both clinically as well as with urodynamic testing. The prevalence of MUI is highly variable and estimated to be between 29 and 61% of incontinent women [2–6].

In epidemiologic studies, women with MUI generally have more severe symptoms and tend to be more bothered by their symptoms than women with pure stress or pure urge components. Consequently, women with MUI are more likely to present for treatment [5]. Typically, clinicians treat the component of MUI which is most symptomatic, most bothersome, and most readily treated. Thus, while women with predominant stress incontinence undergo surgical treatment, those with predominant urge incontinence are treated with medicine and pelvic floor muscle therapy. However the optimal treatment for women who experience significant and bothersome symptoms of both stress and urge incontinence is not known. Without clear clinical guidelines for clinicians, such women with MUI are subject to a wide variety of treatment approaches without any corroborative scientific evidence. To date, there have been no studies in which the efficacy of the two most common treatment approaches to MUI (surgical vs. conservative therapy) has been compared. Nor has it been determined whether or not both surgical and nonsurgical treatment is always necessary.

Methods

Study design issues

The study population consists of an eligible subset of community-dwelling women who presented for the treatment of MUI and met eligibility requirements (Table 1). The flow of subjects in this study is shown in Figure 1.

Reaching consensus and equipoise

As expected, in the absence of high-quality scientific evidence, investigators held various opinions regarding equipoise of the two treatment arms. Many clinicians believe that even if the stress component of MUI is significant, surgical intervention may increase the risk of the urge component being further aggravated postoperatively. According to this approach, the urge component should be initially treated nonsurgically with medication with or without the addition of pelvic floor therapy and behavioral modification. If the stress component persists, it should then be managed surgically with procedures such as retropubic bladder neck suspension or suburethral sling. However, it is not known how much women with MUI actually benefit from surgery or even whether they experience worse urinary incontinence due to an exacerbation of their urge symptoms after surgical treatment of stress incontinence [7–9]. The few studies supporting the concern that UUI worsens after stress incontinence surgery are mostly retrospective, have limited sample sizes, and have inconsistent definitions of urge incontinence.

In patients with pure SUI, the rate of onset of *de novo* irritative voiding symptoms (urgency, frequency, urge incontinence) after incontinence surgery ranges from 12–25.9% [7,8,10] but may be lower with mid-urethral sling procedures [11]. The mechanisms responsible for the development of these symptoms are not well understood [12], and there have been no consistent urodynamic parameters or symptoms that predict or correlate with postoperative *de novo* urge incontinence.

Nonsurgical treatment for patients with MUI typically consists of anticholinergic medications and/or behavioral therapy, although there is no clear guidance regarding the optimal choice of medication [13]. A recent Cochrane review of 13 trials of pelvic floor muscle exercise found that these treatments were equally effective for SUI and MUI compared to no treatment or placebo [14]. The use of anticholinergic medications also improves symptoms in subjects with MUI. Recently, the multicenter BE-DRI trial performed by the UITN showed that behavioral therapy incorporating pelvic floor muscle training in addition to medicine was slightly better than medicine alone in improving urinary symptoms in patients with urge urinary incontinence [15]. William *et al.* investigated the use of pelvic floor therapies for mixed incontinence but did not detect improvements in UI despite improvements in pelvic floor function [16]. Thus, the literature supports the concept that optimal nonsurgical management of urge symptoms should incorporate both medicine and pelvic floor muscle therapy.

Some observational studies suggest that both stress and urge incontinence will be objectively cured (no stress or urge incontinence) in up to 85% of women with MUI managed surgically with a mid-urethral sling [10]. Indeed, objective cure rates for women with SUI and MUI in these studies are similar [9]. Thus, proponents of the initial surgical approach suggest that patients with MUI should be treated with surgery first and then if urge symptoms persist, treatment with nonsurgical therapy should follow. Interestingly, however, in the same studies, the subjective cure rates for patients with MUI tend to be lower than those with pure SUI, although not statistically significant due to small sample sizes. Others have demonstrated that the lower subjective cure rates for women with MUI are associated with a persistence of urge incontinence symptoms [17,7]. Several studies indicate that urge incontinence is the major

cause of post-surgical dissatisfaction in patients following stress incontinence or prolapse repairs [18,19]. In some cases, the severity of the urge symptoms can be debilitating enough to warrant a revision or reversal of the continence procedure.

Pragmatic versus efficacy study design

An initial major decision was selection of an appropriate design for this study. The group extensively discussed the intention to apply the findings of the MIMOSA study to as broad a population as possible. The UITN's prior studies had been designed as efficacy trials; however a major difference in the MIMOSA trial was that we were interested in comparing treatment approaches that included a range of interventions, rather than the specific interventions *per se*. Consistent with the study objective to provide scientific evidence with which to guide clinical decisions about treatment for MUI, we selected a practical clinical trial design. The study design, scientific aims, and hypotheses of a practical clinical trial are formulated based on information needed to make a clinical decision [20,21]. Distinctive features of a practical clinical trial include selection of clinically relevant interventions for comparison; a diverse study population (broad inclusion and minimal exclusion criteria); recruitment from a variety of practice settings; and collection of data on a broad range of health outcomes, including patient-reported and cost outcomes [22]. To maintain clinical relevance and generalizability, this practical clinical trial design is reflected in the less stringent eligibility criterion, inclusion of a wide range of treatments, nonstandardization of treatments, and diverse outcome (primary and secondary) measures in the study design for MIMOSA.

This decision then required the investigators to identify a list of allowable interventions for each treatment arm (medical or surgical) without the need to standardize the intervention within the group. Allowable interventions were determined by standard of care and available scientific evidence. *A priori*, we determined that this list could be expanded and contracted as additional scientific evidence became available throughout the trial. The decision to have a list of allowable interventions had the benefit of allowing clinicians to provide the medical or surgical treatment of their choice, as long as that practice was an allowed intervention.

Achieving a consensus for allowable interventions in the nonsurgical arm proved to be more challenging than in the surgical arm as practices for the treatment of urge incontinence varied widely. Indeed, treatments ranged from writing a prescription for a drug with a handout on behavioral strategies and pelvic floor muscle exercises to a more comprehensive program consisting of drug, behavioral therapy, and exercises with a trained interventionist. In the end, the group decided that for equipoise, the treatment in this arm should be based on scientific evidence. Thus, the nonsurgical treatment included two components: pharmacological therapy with any FDA-approved urge incontinence medication in approved doses and behavioral therapy consisting of at least four visits in 6 weeks with a site-specified and approved interventionist. Participants learned pelvic floor muscle exercises and strategies to suppress urge and stress incontinence. Use of printed or video information regarding medical side effects (by class of medication, not drug-specific), behavioral strategies to suppress stress and urge incontinence symptoms, and guidelines for fluid management were allowed if deemed appropriate by the individual site interventionists.

Surgical treatment consisted of the surgeon's choice of one of the evidence-based stress incontinence procedures, including mid-urethral slings (TVT, TOT, TVT-O), fascial slings, and Burch colposuspension. Based on emerging empirical evidence throughout the study period, a surgical technique work group maintained a list of approved procedures.

Cross-over versus parallel groups

The utility of a cross-over design was initially discussed, but not adopted as it would only apply to a subgroup of the population. The investigators believed that it was appropriate to assess participant-reported outcomes at 3 months, because peak improvements from both treatment approaches should be evident at that time. Additional clinical care for participants who were dissatisfied with the outcome of initial treatment was offered after the 3-month assessment as clinically appropriate. Although investigators believed that many participants would 'cross over' and receive the other type of treatment, this was considered a clinical phenomenon of interest in this study. That is, based on clinical experience, we expected that some participants would receive both types of treatment in order to manage the MUI symptoms. Consistent with the study's objectives, we wanted to know if one of the two initial treatment approaches was more likely to obviate the need for further treatment while successfully managing the symptoms. The participant's assessment of treatment outcome was measured again at 6 months post-randomization to capture her evaluation of the complete treatment experience.

Selection of primary outcomes

The investigators debated whether objective or patient-reported measures were most clinically relevant for this trial. While objective data (voiding diary or pad test) would give a standardized measure of continence status, the investigators agreed that with the complexity of issues facing women with MUI, a woman's subjective assessment of her continence status would be more meaningful to both clinicians and the general population afflicted with this condition. In this way, consensus was reached to base treatment outcomes on participant report, a trend recently adopted by the Food and Drug Administration (FDA). The primary outcome measures include the Patient Global Impression Index of Improvement (PGI-I) and the Patient Global Impression Index of Severity (PGI-S) [23]. The PGI-I is a global, patient-oriented outcome measure that assesses components of both SUI and UI. The PGI-I asks subjects to best describe how one's urinary tract condition (bladder) is now, compared to how it was before treatment for urinary leakage. Response choices are: (1) 'very much better', (2) 'much better', (3) 'a little better', (4) 'no change', (5) 'a little worse', (6) 'much worse', and (7) 'very much worse'. Construct validity of the measure has been demonstrated in incontinence trials.

The PGI-S is a global assessment of severity of the patient's urinary condition at baseline and after treatment. The scale asks for the best description of how one's urinary tract condition is now. Response choices are: (1) 'normal', (2) 'mild', (3) 'moderate', and (4) 'severe'. Construct validity has also been established for this measure.

We considered outcomes dichotomously as 'optimal' and 'suboptimal'. Optimal outcome was defined as a participant report of incontinence as 'much better' or 'very much better', and a participant report of 'normal' or 'mild' urinary symptoms. Suboptimal outcome was defined by the occurrence of one of the following at 3-months post-treatment and at 6-months post-randomization: participant report of incontinence as 'a little better', 'no change', 'a little worse', 'much worse' or 'very much worse', or patient report of 'moderate' or 'severe' urinary symptoms.

Secondary outcomes were selected to capture other aspects of participant pelvic health and quality of life. Based on experience with previous trials, investigators worked diligently to balance robust data collection against participant burden. The final secondary outcomes include symptom bother (Urogenital Distress Inventory Questionnaire), incontinence-specific quality of life (Incontinence Impact Questionnaire[24,25]), general health-related quality of life (Short Form-12 Health Survey [26]), sexual function (short form of the Prolapse/Urinary Incontinence Sexual Questionnaire [27]), voiding behavior and incontinence episode frequency by 3-day voiding diary, and satisfaction with treatment outcome measured on a 5-point Likert scale (very

dissatisfied to very satisfied) that asks the participant to rate her satisfaction about how the treatment has affected (1) urine leakage; (2) urine leakage related to feeling of urgency; (3) urine leakage related to physical activity, coughing, or sneezing; and (4) frequency of urination.

The UITN investigators had significant discussion on the best method to capture the clinical care of participants following the initial randomization. Consensus was reached to capture all additional treatments beyond the assigned treatment, besides economic and cost-utility measures (for both direct and indirect medical costs). As with all UITN studies, any treatment complications and morbidity were collected and coded using a slightly modified version of the validated system of Dindo *et al.* [28]. Figure 2 displays the schedule of measurements.

Timing of outcome assessments

Time from decision to implementation of medical versus surgical management differs. While treatment with medicine can start virtually immediately, scheduling and undergoing a surgery often takes a matter of weeks. In an effort to limit time from randomization to surgery, the investigators required that the assigned treatment approach should be initiated within 6 weeks following randomization. However, even with this requirement, the intervals between randomization and receipt of assigned treatment still would vary, thus posing a significant design challenge with regard to determining the optimal time for the measurement of the primary outcomes. Consensus was eventually reached when the investigators recognized two different intervals with different starting points.

The post-randomization interval was based on the day of randomization whereas the post-treatment initiation interval was based on the actual time the intervention was initiated. This allowed clarity for an *a priori* time point treatment-outcome evaluation at 3 months post-treatment initiation and 6 months post-randomization. The post-randomization time interval was specifically chosen to capture process measures associated with the different interventions such as waiting for surgery, surgical recovery, and the burdens associated with altering work and lifestyle to visit an interventionist and implement assigned therapies. The investigators also wished to avoid measuring primary outcomes when participants were in relatively 'acute' clinical circumstances, such as in the post-operative recovery phase. The investigators planned to avoid measuring participants within 4 weeks of the 6-month assessment because some participants may undergo surgery near the planned 6-month post-randomization outcome point (this would apply to participants undergoing surgery later than the initial index surgery).

Method, timing, and technique of randomization

Participants were randomized to either initial nonsurgical treatment or initial surgical treatment approach. Random assignment, stratified by surgeon using permuted blocks, to one of the two treatment approaches was accomplished by an automated randomization system at the Biostatistical Coordinating Center (New England Research Institutes). As with the prior randomized surgical studies of the UITN, a back-up system of randomization using sealed envelopes was available in case of technical problems. Participants and interventionists were not blinded to treatment assignment.

Assessment of study feasibility

Due to the universal concern that recruitment to a trial with a surgical and a nonsurgical arm would be challenging, the investigators planned a feasibility phase for this trial. The first 5 months of the study were used to assess the enrollment capability of the study sites in order to ensure timely completion of the trial. The numeric thresholds for the feasibility phase were based on recruitment experience in prior trials, such that UITN investigators expected that the nine clinical sites could recruit at least 26 patients per month in total. To ensure that all sites would start recruitment at the same time, the trial was not initiated until all nine clinical sites

had received protocol approval, that is, in November, 2008. Enrollment was stopped in March 2009 due to the low number of randomized participants ($N = 27$) in relation to the number of patients screened ($N = 1198$) and approached for study enrollment. As subjects remain in follow-up, a separate report will describe the outcomes of the feasibility study. The investigators felt that recruitment was difficult for two reasons. First, in our effort to find equipoise, we likely overestimated the availability of the intended study population. Second, we found that some of the potentially eligible subjects were unwilling to undergo randomization to medical versus surgical treatments.

Discussion

The design and conduct of the feasibility phase of the MIMOSA trial posed significant challenges. These challenges included: (1) selection of the practical paradigm; (2) refining inclusion/exclusion criteria to offer equipoise; (3) selection of feasibility sample size; (4) recruitment challenges for two divergent treatment approaches (medical vs. surgical), and (5) ethical and methodological issues. Consensus among investigators was reached regarding the importance of identifying the optimal initial treatment approach for women with MUI; however, there were significant challenges in reaching consensus on the specific design of the trial, the selection of outcome measures, and whether the patients would be willing to randomize to two disparate treatment arms.

The investigators were often challenged to revisit design decisions based on the paradigm of a practical trial. Ultimately, the practical clinical trial design is reflected in the less-stringent eligibility criterion, inclusion of a wide range of treatments, nonstandardization of treatments, and diverse outcome (primary and secondary) measures in the study design.

The decision to use participant assessment outcomes for the primary outcome is consistent with the pragmatic design of the trial. The condition of MUI has signs and symptoms of both urge and stress urinary incontinence. An outcome tool useful in measuring efficacy of SUI treatments such as a standardized stress test would not be a valid outcome tool to assess efficacy of UUI treatment. In a pragmatic trial, we selected tools that reflect a relevance to the participant's experiences in everyday life. Participants do not necessarily differentiate between stress and urge symptoms when they experience incontinence. They know only that they leak urine.

Despite the acceptance of each treatment approach in clinical practice as standard therapy for MUI, the investigators recognized the potential difficulty in recruiting patients for randomization to such different treatment arms. Others have attempted trials that compare surgical versus nonsurgical treatment groups. In the gynecologic literature, the Dysfunctional Uterine Bleeding Intervention Trial (DUBIT) enrolled subjects with a history of intractable dysfunctional uterine bleeding who had failed medical therapy. They were to be randomized to three divergent, although commonly utilized, treatment approaches including hysterectomy, endometrial ablation, and medical management [29]. Despite diverse recruitment strategies, only five subjects enrolled after 6 months and the study design had to be changed to an elective treatment cohort design with a randomization component.

The investigators in the Medicine or Surgery (Ms) trial successfully recruited 63 women for randomization to hysterectomy versus medical management. However, they were forced to lower their sample size and increase their effect size after the trial had started due to low recruitment in the early years of the study. In the urology literature, the PIVOT trial is a pragmatic RCT comparing radical prostatectomy to expectant management for localized prostate cancer [30]. The original sample size had been calculated at 2000 patients to provide 90% power to detect a 15% relative reduction (5% absolute reduction) in all-cause mortality.

However, recruiting difficulties forced them to revise the initial power calculation. Based on the characteristics of the first 200 enrollees, they that estimated an enrollment of 740 men could provide 85% to detect a 25% relative reduction (15% absolute reduction) in all-cause mortality. A successfully completed RCT comparing surgical versus nonsurgical treatment was performed in studying treatment of knee osteoarthritis [31]. In this trial, 277 patients were screened and only 31 declined to enroll in the trial showing that subjects may be willing to undergo randomization between surgical and nonsurgical arms.

Nevertheless, we felt there was potential for both providers and subjects to be resistant to randomization to a surgical versus nonsurgical approach and therefore thought it important to determine feasibility prior to committing to a full-scale trial. The feasibility phase was a critically important design feature of this trial.

Summary and future research

Although we were unable to meet a *priori* feasibility criteria in conducting a novel and challenging trial to compare two treatment approaches for women with MUI, we hope that the lessons learned by our group would benefit other trial groups planning trials with similar features.

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Appendix A: MIMOSA

Format for crediting sites and funding in publications

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Figure 1.
MIMOSA study eligibility and participant flow

	Screening*	Baseline*	Process measures	3 months post-treatment	6 months post-randomization
MESA	X			X	X
UDI-6 or PFDI	X				
PGI-S	X			X	X
Physical examination		X			
Voiding diary		X		X	X
UDS		X			
History		X			
Sociodemographics		X			
Medication audit		X		X	X
Comorbidities		X		X	X
UDI		X		X	X
IIQ-7		X		X	X
SF-12		X			X
PISQ-12		X		X	X
PHQ-9		X		X	X
Costs		X			X
HU13		X			X
Goals		X		X	X
Initial treatment data			X		
AEs			X	X	X
Additional treatment				X	X
PGI-I				X	X
Difficulties				X	X
Satisfaction				X	X

* Measure must be repeated if patient is not randomized within 6 months of completion.

Figure 2.
Schedule of measurements

Table 1**Inclusion and exclusion criteria**

Inclusion criteria	
1	Female
2	Mixed UI as evidenced by stress and urge symptoms reported on MESA (either percent of urge-type symptoms > the percent of stress-type symptoms or urge symptom score ≥ 7) followed by report of 'moderate' or 'great' bother to questions 2 and 3 of the UDI-6
3	Moderate or severe UI as evidenced by the corresponding response on the PGI-S
4	Incontinence symptoms present for at least (3) months ^a
5	Bladder capacity ≥ 200 cc (by any method)
6	Urodynamic stress incontinence
7	Eligible for both treatment interventions
8	Available to start intervention within 6 weeks
9	Negative urine dipstick (negative result = trace or less for leukocytes and nitrites)
10	Available for 12 months of follow-up and able to complete study assessments as per clinician judgment
11	Signed consent form
Exclusion criteria	
1	Age <21 years ^a
2	Currently undergoing or recommended to undergo treatment of pelvic organ prolapse
3	Other indicated/planned concomitant surgery
4	Pregnant or has not completed child-bearing ^a
5	<12 months post-partum ^{a,b}
6	Active malignancy of cervix, uterus, fallopian tube(s), or ovary > stage I, or bladder of any stage
7	Current catheter use
8	Unevaluated hematuria
9	Participation in another trial that may influence the results of this study

^aPatient can be re-screened after respective time interval has been met.

^b'Partum' is defined as a delivery or other termination that occurs after 20 weeks gestation.