The <u>T</u>rial <u>O</u>f <u>M</u>id-<u>U</u>rethral <u>S</u>lings (TOMUS): Design and Methodology

Urinary Incontinence Treatment Network (UITN)[*]

KEY WORDS: mid-urethral sling, randomized surgical trial, tension-free vaginal sling, transobturator sling, urinary incontinence, urodynamics

ABSTRACT

Objective: Mid-urethral slings (MUS) are increasingly common surgical procedures for the treatment of stress urinary incontinence (SUI) in women. There are currently no adequately powered trials with sufficient length of follow-up comparing the efficacy or safety of the transobturator and retropubic MUS. As a result, no selection criteria are available to guide surgeons or patients. This article describes the methodology and rationale for the Trial Of Mid-Urethral Slings (TOMUS).

Patients and Methods: The primary aims of this randomized controlled trial are to compare subjective and objective success rates for urinary incontinence (UI) at 12 and 24 months following retropubic and transobturator MUS procedures. Secondary aims are to compare the resolution of overall and stress-specific UI, morbidity, the time to adequate voiding, satisfaction, and quality of life in the 2 groups. TOMUS will also assess the clinical utility of pre-operative urodynamics in women undergoing MUS procedures. The primary outcome will be obtained at 12 months and 24 months. The definition of treatment success is 2-fold. *Objective treatment success* is defined by a negative stress test, a negative 24-hour pad test, and no retreatment for SUI. *Subjective treatment success* is defined by no self-reported leakage in a 3-day diary, no self-reported SUI symptoms, <u>and</u> no retreatment for SUI. Enrollment began April 2006 and is expected to be complete in 2 years.

Conclusions: The TOMUS trial is designed to provide outcome and safety information to pelvic surgeons and their patients on the 2 most commonly performed MUS techniques.

INTRODUCTION

New surgical therapies for the treatment of stress urinary incontinence (SUI) are developed and offered as standard of care without adequate scientific evaluation of their effectiveness or safety. Estimates place the number of different surgical procedures for SUI between 100 and 150.[1,2] The mid-urethral sling (MUS) procedures were developed in an effort to provide patients with a less invasive therapeutic option for surgical treatment of SUI than the traditional sling and Burch procedures, without compromising efficacy. The retropubic mid-urethral sling (RMUS) was first introduced by Ulmsten[3] in 1996 as the tension-free vaginal tape (TVT) procedure and has become one of the predominant surgical

procedures for treating SUI. Subsequently, a transobturator approach to the MUS (TMUS) was developed as a potentially safer alternative to the RMUS by avoiding the retropubic space and instead passing trocars through the obturator canal.[4] While early data suggest similar efficacy for the 2 approaches, the data are from case series, non-randomized trials and underpowered randomized clinical trials (RCT) not designed to adequately assess differences between the 2 procedures.[5-9]

The 1997 American Urological Association Surgical Treatment of Stress Urinary Incontinence Guidelines emphasized that the urinary incontinence literature was insufficient to compare surgical procedures performed for the treatment of SUI.[10] More recently, Nygaard and Heit[11] emphasized the importance of evaluating new therapies in randomized clinical trials before accepting them into general clinical use. It is critical to compare the efficacy and safety of the retropubic and transobturator approaches to the MUS, given the limited efficacy data and the rapid increase in the number of TMUS procedures being performed.

This paper describes the design and methodology of a multicenter randomized surgical trial comparing the efficacy and safety of retropubic and transobturator MUS procedures. Results of this trial will allow clinicians to provide evidence-based outcome and safety data to women with SUI who are considering minimally invasive anti-incontinence procedures.

METHODS

TOMUS (Trial Of Mid-Urethral Slings) is being conducted by the Urinary Incontinence Treatment Network (UITN), a cooperative network consisting of urologists and urogynecologists at 9 clinical centers and a biostatistical coordinating center. The UITN is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Child Health and Human Development (NICHD). An independent 11-member Data Safety and Monitoring Board (DSMB) meets biannually to review the conduct and safety of the trial.

Study Design

TOMUS is a 2-arm, unmasked, multicenter RCT (Figure 1) comparing RMUS to TMUS. There are 2 primary aims: to compare the (1) objective and (2) subjective success rates of the 2 procedures for the resolution of UI at 12 and 24 months. The *a priori* primary endpoint for evaluating success is at 12 months. Secondary aims include assessment of complications, resolution of overall and stress-specific UI, patient bother from UI symptoms, quality of life (QOL), patient satisfaction, sexual function, and time to resumption of normal activities. A separate secondary aim is to assess the clinical utility of preoperative urodynamics.

Patients are randomized in the operating room after the administration of anesthesia using a telephone automated randomization system at the biostatistical coordinating center. Each site has sealed envelopes containing random assignments as a back-up system. Randomization is stratified by clinical site, using permuted blocks.

The protocol was approved by the DSMB of the UITN and Institutional Review Boards of all participating centers. Written informed consent is obtained in all women who enroll in the study. The trial will take approximately 4 years (2 years to recruit and 2 years minimum follow-up) and began enrolling patients in April 2006.

Study Population
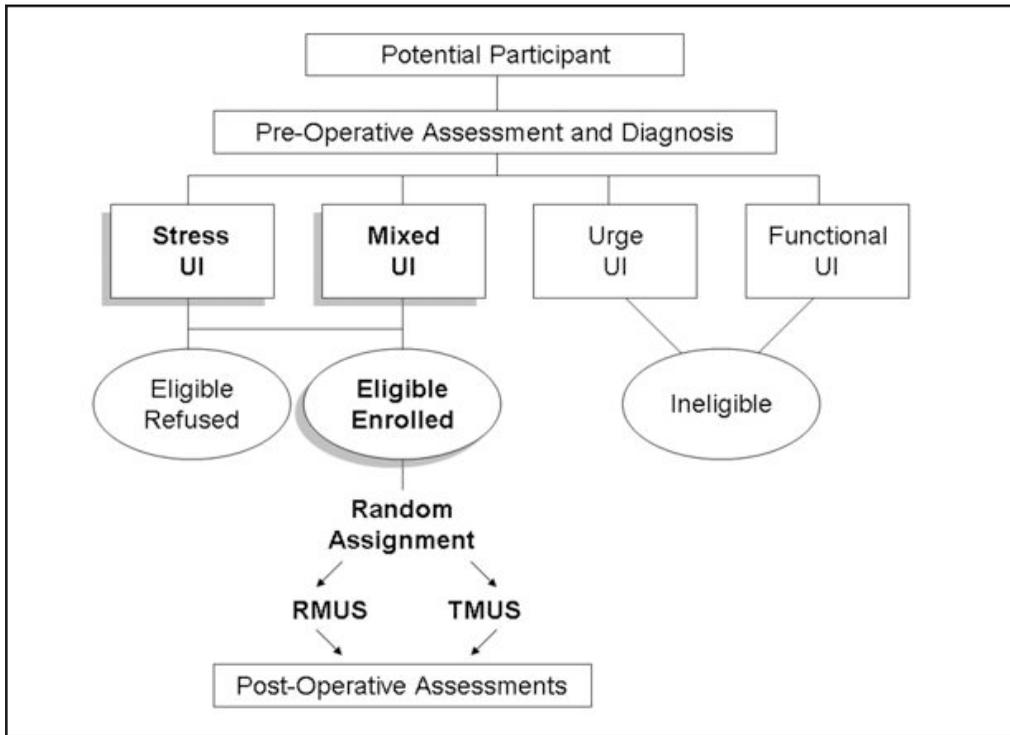
Women diagnosed with stress predomi-

Figure 1. Patient flow diagram. UI = urinary incontinence; RMUS = retropubic mid-urethral sling; TMUS = transobturator mid-urethral sling.

nant urinary incontinence by symptoms on questionnaire and a positive standardized stress test and who desire surgical treatment are eligible. Inclusion and exclusion criteria are listed in Table 1.

Primary Outcomes
Treatment success at 12 months post-surgery will be assessed both objectively (clinically) and subjectively (patient report). *Objective treatment success* is defined as a negative stress test, a negative pad test (<15 grams/24 hours), and no retreatment of SUI. *Subjective treatment success* is defined as no self-reported leakage by a 3-day voiding diary, no self-reported stress-type urinary incontinence symptoms, and no retreatment of SUI. Treatment failure can be diagnosed any time after 3 months post-operatively. Re-treatment includes behavioral, pharmacologic, and surgical treatment for SUI symptoms and can occur any time post-surgery.

Assessment Schedule
Data are collected by clinical examination, patient interview, and self-administered survey at in-person visits pre-operatively and at 2 weeks, 6 weeks, and 6, 12, and 24 months post-operatively (Table 2). Patients who require re-treatment for SUI receive the 12-month assessment battery prior to the initiation of re-treatment. Such patients remain in the study for follow-up as scheduled.

Measures
Assessment of urinary incontinence. The presence of urinary incontinence will be assessed with the Medical, Epidemiologic, and Social Aspects of Aging (MESA) questionnaire,[12] a 3-day voiding diary,[13-15] a 24-hour pad test,[16,17] and a provocative stress test standardized to position and a bladder volume of 300 mL.[18]

Other measures. The following measurement tools will be used to assess the

Table 1. Inclusion and Exclusion Criteria.

Inclusion Criteria
- Female
- Self-reported stress-type UI symptoms, of duration ≥3 months[a]
- MESA[b] stress symptom score (percent of total possible stress score) greater than MESA urge symptom score (percent of total possible urge score)
- Observation of leakage by cough and valsalva stress test at a bladder volume ≤300 mL
- Bladder capacity ≥ 200mL
- Post-void residual
  - ≤100 cc with Stage I or lower pelvic organ prolapse
  - >100 cc but ≤500 cc with Stage II-IV pelvic organ prolapse

Exclusion Criteria
- Age <21 years[a]
- Non-ambulatory (ambulatory with assistive devices allowed)
- Pregnancy by self-report or positive pregnancy test, or self-reported intention to ever become pregnant
- Current chemotherapy or current or history of pelvic radiation therapy
- Systemic disease known to affect bladder function (ie, Parkinson's disease, multiple sclerosis, spina bifida, spinal cord injury or trauma)
- Urethral diverticulum, current or previous (ie, repaired)
- Prior augmentation cystoplasty or artificial sphincter
- Implanted nerve stimulators for urinary symptoms
- History of synthetic sling for SUI; history of vaginally placed synthetic mesh during reconstructive surgery
- <12 months post-partum[a,c]
- Laparoscopic or open pelvic surgery <3 months[a]
- Current evaluation or treatment for chronic pelvic pain (painful bladder syndrome)
- Participation in another treatment intervention trial that might influence the results of this trial
- Need for concomitant surgery requiring an open or laparoscopic abdominal incision, use of synthetic graft material or use of biologic graft material in the anterior compartment.
- Enrollment in the Urinary Incontinence Treatment Network's other trials

[a]Patient can be rescreened after respective time interval has been met.
[b]Medical, Epidemiologic, and Social Aspects of Aging questionnaire.
[c]"Partum" is defined as a delivery or other termination that occurs after 20 weeks gestation.

secondary outcomes: QOL by the International Consultation on Incontinence Questionnaire[19] and Incontinence Impact Questionnaire[20]; symptom bother by the Urogenital Distress Inventory[20]; sexual function by the Prolapse/Urinary Incontinence Sexual Questionnaire[21,22]; treatment satisfaction by a self-administered satisfaction questionnaire[23] and the Patient Global Impression of Severity and Improvement questions[24]; and resumption of normal activities by the Activities Assessment Scale.[25] Sociodemographic and clinical characteristics of the participants are also assessed.

Cost measures. Data will also be collected regarding the use of incontinent aid products using the Incontinence Expense questionnaire,[26] health care utilization,[27] and patient preferences for states of health. Direct costs will be calculated using Medicare resource-based relative value scale charges for physician services as a proxy for societal cost.[28] Utilities (or patient preferences) associated with urinary incontinence will be measured with the Health Utilities

Table 2. Schedule of Measurements.

	Baseline (pre-op)	Op	2 Weeks[a]	6 Weeks[a]	6 Months	12 Months[b]	24 Months
Primary Outcomes							
Stress test	✓[c]				✓	✓	✓
Pad test	✓[d]				✓	✓	✓
New interventions or re-treatment			✓	✓	✓	✓	✓
MESA questionnaire	✓[d]			✓	✓	✓	✓
Voiding diary	✓[d]				✓	✓	✓
Secondary Outcomes							
Quality of life	✓[d]				✓	✓	✓
Patient bother	✓[d]		✓	✓	✓	✓	✓
Voiding function							
Post void residual	✓[c]	✓	✓	✓	✓	✓	✓
Self-report	✓[d]		✓	✓	✓	✓	✓
Pain							
Self-report[e]	✓[d]	✓	✓	✓	✓	✓	✓
Exam	✓[d]		✓	✓			
Patient satisfaction					✓	✓	✓
Resumption of activities	✓[d]		✓	✓	✓		
Sexual function	✓[d]				✓	✓	✓
Complications/morbidity		✓	✓	✓	✓	✓	✓
Urodynamics	✓[c]					✓	
Urine dipstick	✓[d]		✓	✓	✓	✓	✓
Cost measures	✓[d]					✓	✓
Independent Variables							
Sociodemographic	✓						
History and physical	✓[d]				✓	✓	✓
Q-tip test	✓[c]						
Medication audit	✓[d]		✓	✓	✓	✓	✓
Intervening Variables							
Prolapse assessment[a]	✓[d]					✓	✓
Operative measures		✓					
Depression	✓[d]				✓	✓	✓
Patient expectations	✓[d]						

MESA = Medical, Epidemiologic, and Social Aspects of Aging.
[a]Visit frequency between 2-6 weeks will depend on voiding function.
[b]Or at time of treatment failure, if earlier. If patient is surgically retreated and therefore has urodynamic studies prior to 12-months as part of treatment failure battery, urodynamic studies are not done again at 12-months.
[c]Measure must be repeated if patient is not randomized within 12 months of completion.
[d]Measure must be repeated if patient is not randomized within 6 months of completion.
[e]Post-operative self-report: daily until pain resolves or 4 weeks post-op.

Index Mark 3[28,29] and willingness to pay for urinary incontinence improvement.[30]

Complications. Complications are specifically defined in the study protocol to ensure consistency in reporting between investigators and between sites. A standardized assessment of complica- tion severity across sites will be per- formed using a validated severity classi- fication system.[31] In order to detect small differences between the RMUS and TMUS procedures, post-operative assessment will begin immediately after discharge from the hospital and contin-

Table 3. Standardized Urodynamic Studies.

Test	Measures
Non-instrumented uroflow	Maximum flow rate
	Mean flow rate
	Time to maximum flow
	Voided volume
	Post void residual
	Flow pattern
Urethral pressure profile	Maximum urethral closure pressure
	Functional urethral length
Cystometrogram	Baseline and capacity pressures
	First desire
	Strong desire
	Maximum cystometric capacity
	Compliance
	Valsalva leak point pressure
	Involuntary detrusor contraction
Pressure flow	Maximum flow rate
	Detrusor pressure at maximum flow
	Time to maximum flow
	Voided volume
	Voiding mechanism
	Post void residual

ue for 2 weeks. Post-operative voiding will be measured in many dimensions including patient questionnaire, objective documentation of the return to normal voiding, long-term assessment of urodynamic variables, and the need for treatment. Differences in pain severity and duration between the 2 procedures will be measured using a daily pain diary and a physical examination assessment at baseline, and at 2 and 6 weeks after surgery. The 4-item McCarthy pain scale[32] assesses severity and degree of bother from pain at rest and with various activities after surgery.

Urodynamic studies (UDS). Urodynamic tests are performed preoperatively and at 12 months in all patients (Table 3). Standardized testing procedures and interpretation guidelines were developed by a urodynamics work group utilizing the methods, definitions, and units recommended by the International Continence Society Standardisation Committee of Good Urodynamic Practice and the Good Urodynamics

Practice Guidelines.[33,34] The UITN has established excellent inter-rater reliability between local and central reviewers for UDS parameters in previous network trials using similar UDS methods.[35]

To ensure that pre-operative UDS results do not influence patient selection, surgical technique, or post-operative management of voiding symptoms, pre-operative UDS will be performed after enrollment. The UDS tracings will be interpreted by a non-treating, study surgeon while the treating surgeon remains masked to UDS results. Post-operatively, the treating physicians may request to review the pre-operative UDS in order to treat post-operative symptoms; however, they will be asked to specify their reasons for the review and their diagnosis before and after reviewing the UDS.

Study Treatments
The specific MUS procedures performed in this study are limited to the original RMUS procedure, the TVT™

Table 4. Power Calculations Based on Differing Cure Rates.

Common Cure Rate	Range of Equivalence (percentage points)
70%	12
80%	11
90%	8

(Gynecare, ETHICON Women's Health & Urology, Somerville, NJ), and 1 of 2 TMUS procedures, the Tension Free Vaginal Tape–Obturator (TVT-O™; Gynecare) or the Monarc™ (American Medical Systems, Minnetonka, MN). Key aspects of the procedures have been standardized across surgeons and sites to improve internal and external validity. Each surgeon has pre-selected which TMUS technique he/she will use during the study. A study surgeon must have performed a minimum of 5 RMUS and 5 TMUS procedures, and his/her principal investigator must have observed him/her performing the key aspects of each procedure before the surgeon can be approved as a study surgeon.

Concomitant prolapse repair surgery is allowed only if it is performed vaginally and without the use of synthetic graft material. Additionally, no biologic graft material is allowed in the anterior compartment. Surgeons are expected to declare the type of concomitant surgery they plan to perform prior to randomization.

Statistical Analysis
The current study is designed to detect equivalence in the success rates of the 2 procedures within a clinically meaningful range of equivalence (Table 4). Prior studies report 12-month cure rates as high as 90% and 24-month cure rates of approximately 60%-70%. If the 2 procedures have the same underlying cure rate, samples of 250 participants in each group achieve 80% power at a 5% significance level using a 2-sided equivalence test of proportions. An 85%

follow-up is anticipated; therefore, 294 women will be randomly assigned to each surgical arm.

The percentage of women in each treatment arm who meet the objective and subjective definitions of success at 12 and 24 months post-treatment will be computed using Kaplan-Meier time-to-event methods, controlling for study site. To test the equivalence of the 2 percentages at each follow-up time point, the difference in percent success with 95% confidence limits will be computed. The null hypothesis will be rejected and the procedures will be considered equivalent if the confidence interval lies entirely within the range -0.12 to +0.12.

Analysis of continuous outcomes such as the QOL subscales will be based on change from baseline. Prognostic models will be developed using baseline urodynamic testing results and other baseline covariates to explore the extent to which baseline measures can be used to predict surgical success. Time-to-event methods will be utilized to characterize time to normal voiding.

The decision to stop the trial early due to safety or efficacy concerns is at the discretion of the DSMB. An interim statistical analysis of the primary study hypothesis will be performed when approximately half of the expected failures have occurred. Repeated confidence intervals, as recommended by Jennison and Turnbull,[36] were selected for use in this study because of the flexibility in the situation where the formal stopping rule may not be followed. Interim monitoring of treatment failures will be conducted using Kaplan-Meier time-to-event analysis to estimate the

cumulative probability of failure. The methodology of Lan and DeMets[37] will be used to implement an O'Brien-Fleming stopping boundary for this monitoring. The stopping boundary will determine the level of confidence for the interim confidence interval calculation.

DISCUSSION

Choice of MUS Technique

The currently available MUS procedures attempt to distinguish themselves by highlighting differences in technique and type of sling material. How these differences impact the efficacy and/or morbidity of the procedures is not known. TOMUS is designed to isolate one of these variables, the anatomic location (retropubic versus transobturator) through which the trocars are passed during placement of the sling, and to compare the efficacy and morbidity of these approaches in the treatment of SUI.

The original RMUS is cited in over 541 published articles with overall long-term objective success rates of 81% at 91 months.[38] These success rates are similar to those reported for the Burch colposuspension and rectus fascia slings.[39,40] Randomized clinical trials comparing the TVT with the allogenic suburethral sling,[41] laparoscopic Burch,[42,43] and open Burch procedures[44,45] demonstrate similar success rates for TVT versus these traditional procedures for the treatment of SUI. Complications such as retropubic hematoma, bladder injury, and rarely more life-threatening injuries to bowel or major blood vessels, while infrequent, have been reported.[5,46,47] Modifications to the TVT have been in response to these complications and clinicians' concern about passing trocars blindly through the retropubic space. Modifications have included both suprapubic and transobturator approaches. The limited comparative studies between TVT

and the suprapubic approach have not demonstrated any advantage over the TVT with regard to morbidity, and they provide conflicting data with regard to efficacy.[48,49]

The transobturator approach, on the other hand, offers the potential advantage of avoiding the retropubic space completely. Transobturator MUS procedures are performed by 1 of 2 techniques, differing only in the direction the trocar is passed through the obturator foramen: the lateral to medial technique described by Delorme[4] or the medial to lateral technique described by de Leval.[50] Theoretically, the direction the trocars are passed can result in differences in the size of the vaginal incision, the amount of peri-urethral dissection, and the proximity of the trocar to the obturator neurovascular bundle as it passes through the obturator foramen. A 3-arm design comparing the 2 TMUS approaches to each other as well as to the RMUS approach was considered. However, without evidence or plausible reasons that one of the TMUS techniques was better, the increased cost and recruitment time needed for the larger sample size could not be justified.[51,52]

Choice of Sling Material

The current MUS products utilize a variety of mesh materials, each with specific biomaterial characteristics. Specific mesh characteristics are thought to facilitate macrophage response and tissue in-growth and thus are theoretically associated with lower erosion and/or infection rates. These characteristics include knitted polypropylene material, pore size greater than 75 micrometers, minimal interstices, and low density.[53] The TVT™ mesh as well as 6 of the other transobturator mesh materials meet those criteria. Papas et al[54] performed biomechanical analyses on the 6 transobturator mesh materials and compared the following biomaterial characteristics to the TVT:

tensile behavior, structural integrity, textile properties, macroscopic knit pattern, mesh edges, and mesh modifications designed to improve intra-operative handling (eg, tensioning suture, heat sealing). This analysis revealed marked differences between the TVT mesh and all but 1 (Monarc) of the 6 other mesh materials. Other investigators have reached similar conclusions with regard to the similarities between MUS mesh materials.[55] Whether these mesh characteristics are important for safety and/or efficacy in SUI surgery is not known. Nevertheless, because they could potentially confound the primary or secondary outcomes, the decision was made to exclude the other 5 mesh materials from this trial.

In selecting which MUS products to include in the TOMUS trial, we chose to use the gold standard MUS as the control and to limit the confounding variables to the location of the trocar passage. Therefore, the MUS products that will be utilized in the TOMUS trial are limited to the TVT in the retropubic group and either the TVT-O or the Monarc in the transobturator group.

Outcome Measures
The optimal method for assessing outcomes after SUI surgery remains unclear, especially because patient satisfaction and traditional objective cure measures are not well correlated. There are limited data using the global satisfaction and improvement measures as a primary outcome after continence surgery. The TOMUS study uses a composite primary outcome measure, with objective and subjective components, similar to the outcome measures utilized in the UITN's recently completed Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) trial[23] comparing the Burch procedure to autologous fascial slings. It is hoped that the use of similar outcome measures, standardized

across all clinical sites, will better compare the mid-urethral sling outcomes with the more traditional procedures.

There is an increasing focus on patient satisfaction when treating QOL disorders such as incontinence. Three validated condition-specific QOL instruments[20] and 2 satisfaction measures[19,24] will capture the impact of incontinence on everyday life; the impact of incontinence on various activities, roles, and emotional states; and the bother from incontinence symptoms. Little is known about the effect of urinary incontinence or continence surgery on sexual function. Sexual function, bowel function, and return to normal activities will be captured with validated instruments.[21,25] The increasingly important economic impact of incontinence and treatment outcomes will be measured as it was in the SISTEr trial.

Complications and known side effects of surgery can dramatically impact patient satisfaction after treatment of QOL disorders. One of the major priorities of this protocol is to compare the morbidity of RMUS and TMUS. Three of the most common adverse conditions associated with patient dissatisfaction after stress incontinence surgery are voiding dysfunction, urge incontinence, and pain. The TOMUS protocol standardizes definitions for these conditions, the tools used to measure them, and the timing of assessments across all centers.

Urodynamics
Urodynamic studies are commonly performed as part of the preoperative evaluation in women with SUI despite the high cost, the invasiveness of the test, and the controversy regarding their reliability. Advocates claim that UDS provide valuable information in predicting outcomes and identifying risk factors for failure of the procedures. The TOMUS trial affords an excellent opportunity to

examine the clinical utility of pre-operative UDS by limiting the use of UDS data in the pre- and peri-operative decision-making process. This will be accomplished by blinding the surgeon to the pre-operative urodynamics data.

The TOMUS urodynamics protocol will assess the value of the 2 most common urethral function studies, the Valsalva Leak Point Pressure (VLPP) and the Urethral Pressure Profile (UPP). Neither of these measures have demonstrated good correlation with each other, with other measurements of incontinence severity, or with clinical outcomes[56] Pre-operative voiding parameters from non-instrumented flow and pressure-flow studies will be correlated with post-operative voiding function to assess whether post-operative voiding dysfunction can be predicted.

Investigators who value baseline urodynamic information to help manage post-operative voiding complaints or to determine whether symptoms are associated with de novo changes in bladder function will be allowed to utilize the pre-operative UDS after declaring their clinical diagnosis, their treatment plan, and the clinical question they hope to answer with the pre-operative UDS data. They will also record any subsequent changes in management based on the UDS data. Finally, the post-operative UDS will provide insight into the effects of the MUS procedures on bladder function at 1 year post-operatively.

CONCLUSION
TOMUS is a registered, randomized surgical trial designed to compare the efficacy of the most commonly utilized minimally invasive surgical treatments for SUI, the retropubic and transobturator MUS procedures. The primary outcome measure is resolution of UI based on subjective (questionnaire and diary) and objective (pad tests and stress test) assessments. Several secondary outcome measures will also be carefully evaluated, including an analysis of preoperative factors that may suggest favoring one procedure over the other. Masking of study surgeons to all UDS procedures assures that UDS results do not influence choice of surgical treatment. Urodynamic studies will be conducted in a standardized fashion and rigorously reviewed. Therefore, it is also hoped that this study will discern whether pre-operative UDS is associated with outcomes or morbidity in either of the treatment arms.

APPENDIX: THE URINARY INCONTINENCE TREATMENT NETWORK
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