Urinary Incontinence Treatment Network (UITN)

TOMUS:
Trial Of Mid-Urethral Slings

June 5, 2007

A. Background and Rationale for the Study

A.1 Emergence of Minimally Invasive Procedures

New therapies for the treatment of stress urinary incontinence (SUI) are continuously being developed and marketed to clinicians. Some estimates place the number of different surgical procedures for stress incontinence between 100-150 [1, 2]. Many of these procedures have been offered as standard procedures without the proper evaluation as to their effectiveness or safety. The World Health Organization recommended medical technology assessment (MTA) as an essential tool to promote and develop the quality of health care [3]. This is defined as a comprehensive, systematic assessment of the basis for and the consequences of the use of medical technology. The 1997 AUA Panel that developed the Surgical Treatment of Stress Urinary Incontinence Guidelines lamented the fact that so much of the literature was of insufficient quality to compare the various procedures utilized for SUI. At the conclusion of their recent review of SUI, Nygaard and Heit emphasized that new therapies should be studied in randomized clinical trials (RCT) before general clinical use [4]. Unfortunately, this has not been the standard by which treatments are evaluated.

The "gold standard" for the surgical treatment of SUI has traditionally been either the Burch colposuspension or the autologous fascia sling. Although the efficacy for each surgery is consistently reported at 80-85%, both procedures have a number of morbidities. These include the risk of general or regional anesthesia, the need for potential analgesics, a 1-3 day hospital stay, wound complications, prolonged urinary retention, voiding dysfunction, de novo urge incontinence, and up to 4-6 weeks for full recovery. Since SUI is a condition that affects a woman's quality of life, patients ask themselves if this condition warrants the pain and potential morbidity of a surgical procedure. Theoretically, if surgery were less invasive, less morbid, and allowed a more rapid recovery and return to full activity without compromising efficacy, more women might seek surgery.

Minimally invasive sling procedures have been developed in an attempt to fill this need. Ulmsten introduced the Tension Free Vaginal Tape procedure (TVT) in 1996, and it rapidly became the procedure of choice for many clinicians. The TVT utilizes a synthetic prolene mesh placed through vaginal incisions with trocars that are passed retropubically through the abdominal wall. The sling is placed at the level of the mid urethra under no tension. There are now many products on the market that utilize a similar technique. Hereafter we refer to these procedures generically as retropubic mid-urethral sling procedures or RMUS. Efforts to minimize the potential for morbidity associated with passage of the trocar through the retropubic space, while maintaining the minimally invasive nature and high efficacy rates of the procedure, led to development of multiple modifications of the original TVT or RMUS procedures. These include suprapubic, prepubic and transobturator approaches. Currently, multiple transvaginal, suprapubic and transobturator products are being marketed to clinicians. The SPARC (AMS) procedure was the first modification and advocated a suprapubic approach as opposed to a vaginal approach for passage of the trocar. More recently, the transobturator approach to the mid-urethral sling procedure has been described as a potentially safer technique, by passing the trocar through the transobturator canal and avoiding the retropubic space altogether. Hereafter these procedures are referred to as TMUS.

Data suggest that these minimally invasive slings have rapidly become the dominant surgical procedure for treating SUI. Recent estimates from one industry representative indicate that by 2006, over 65% of the incontinence procedures will be done utilizing one of the minimally invasive techniques. TMUS procedures are currently undergoing the highest rate of increase of all minimally invasive procedures. The total number of minimally invasive procedures will increase modestly from 356,000 to 385,000. However, the TMUS approach will increase almost nine-fold, from 11,000 procedures in 2003 to 105,000 in 2005, whereas the number of RMUS procedures will decrease 30%, from 66,000 to 46,000. Using data from the FDA-sponsored MAUDE database, Boyles and Edward reported that between January and September 2004, a total of 30,000 TMUS procedures were registered (including 7,000 ObTape, 17,000 Monarc, and 6,000 TVT-O procedures) [5]. Prior to 2003, these procedures had not been performed in the US. Industry web sites provide limited data regarding growth of these products since their introduction. Mentor states that, as of May 2004, more than 22,000 ObTape procedures had been done worldwide. AMS reported a 6-month increase in Monarc procedures from 3,000 in July 2003 to 11,000 procedures in January 2004. Gynecare introduced their inside-to-out approach obturator system (TVT-O) in January of 2004, while Boston Scientific introduced Obtryx in mid-2004.

The need to compare the efficacy and safety of these two minimally invasive procedures is critical, especially given the limited efficacy data and the rapid increase in the number of TMUS procedures being performed. The UITN is a clinical research network, including nine continence treatment centers and a data-coordinating center, established by the NIH to bring this type of quality investigation to incontinence research. Given the UITN's experience with the SISTEr trial, a RCT comparing the Burch colposuspension and the autologous fascia sling, they are uniquely qualified to study other procedures. Further, the existence of standardized evaluation and follow-up procedures, data collection forms, trained and certified staff, and collaborative working relationships bring cost efficiencies to the conduct of the proposed trial.

A.2 Safety and Efficacy Data

A.2.1 RMUS Procedures

The TVT procedure has been the RMUS procedure studied the most extensively. As of March 2004, there were over 241 publications regarding this procedure in Pub Med. The literature reports high cure rates (85% with up to 7 year follow-up [6]), low morbidity, few complications, use of minimal anesthesia and no overnight hospitalization [7-10]. There is Level 1 evidence that the TVT procedure is comparable in efficacy to the open Burch procedure [11], and has superior efficacy compared to the laparoscopic Burch [12] and the laparoscopic mesh Burch [13]. Given this efficacy and safety profile, as well as the pervasiveness of the TVT procedure in clinical practice, most consider it to be the gold standard for mid-urethral sling procedures. Nevertheless, there continues to be significant concern about the potential for serious complications or even death with this procedure. This concern stems from the potential for inadvertent injury to the pelvic vasculature, bowel or bladder as the trocar is being passed into the retropubic space. This may be of greatest concern in women who have undergone a prior anti-incontinence surgery and may have scarring in the retropubic space. The FDA website (MAUDE) lists a complication rate of 0.002 out of 125,000 TVT procedures recorded for the time period between 1999 and 2003. Unfortunately a number of these were serious including 7

deaths, 6 from bowel injury and one from vascular injury [4]. Bladder injury occurs in about 4-6% of patients and is usually managed easily with a short period of catheter drainage. Less severe morbidity includes prolonged urinary retention and/or voiding dysfunction secondary to obstruction. The true numerator and denominator for these rare but serious complications are unknown since these self-reporting databases are thought to underestimate true complication rates by 10-fold.

A.2.2 Suprapubic Procedures

A prospective multicenter trial was conducted in France that enrolled 104 consecutive women with genuine stress incontinence who underwent placement of a SPARC. The mean follow-up was 11 months. The overall complication rate was 44.2% with a peri-operative complication rate of 10.5% including 11 bladder injuries during passage of the trocars. No vascular or bowel injuries were noted. Objective and subjective cure rates were 90.4% and 72% respectively [14]. A RCT comparing the SPARC and the TVT was performed by Tseng et al [15]. Sixty-two patients were randomly assigned to undergo SPARC or TVT. Although there were no statistically significant differences in complication rates, there was a clinically significant difference of 12 bladder injuries with SPARC and 0 with TVT. Cure rates were not statistically significantly different (80.7% for SPARC and 87.1% for TVT, p=0.706).

A.2.3 TMUS Procedures

The theoretical advantage of the TMUS approach is that it prevents the potential for vascular and intestinal injury associated with the retropubic approach. In addition, it has been theorized that it may be less obstructing than the retropubic approach because of a more lateral fixation of the sling. The first transobturator approach, the UraTape (Mentor-Porges), was developed in France [16]. He described an outside-to-in (medial thigh to vagina) technique of passing the trocar. Within 2 years, 11,000 women in Europe had been treated with either UraTape or its offspring, ObTape (UraTape without the silicone coating on the suburethral portion of the sling). The FDA approved ObTape (Mentor) for use in the US in September 2003. Mentor has now switched from the Obtape to the Aris, which utilizes a different mesh for the same technique. There are a number of other TMUS products currently marketed in the US including Monarc (AMS), TVT-O (Gynecare), and Obtryx (Boston Scientific). Although the TMUS is approved in both the US and Europe, the limited outcome data available on the trans-obturator approach comes primarily from individual case report series of the surgeons who developed the procedure and from a number of multicenter registries in Europe. The procedure has not been evaluated in an adequately powered RCT to assess whether it is as efficacious in treating SUI or as safe as the RMUS.

Delorme et al reported a 90% cure rate with use of UraTape; however, the study included only 32 patients with 12 month follow-up [17]. Two multi-center registry studies provide useful information on the safety and short-term efficacy with the transobturator approach. Costa et al [18] performed The UraTape procedure on 183 women between October 2001 and March 2003 at six centers in France and Belgium. With a mean follow-up of 7 months, they reported a 2.2% complication rate (l bladder perforation, 2 urethral perforations and 1 vaginal perforation) and cure/improved rates of 85.6/7.9% at 3 months and 83/5.4% at 6 months. Cure was defined as an absence of subjective complaint of urine leakage and a negative cough stress test. This group

has maintained an ongoing multi-center TMUS registry, now with 380 patients, that provides the following data (personal communication, Susan Tate, MD):

- 245 have a minimum of 3 month follow-up with a median follow-up of 11 months;
- 85% complete cure, 8% improved, 7% failure;
- Results were the same regardless of maximum urethral closure pressure (MUCP) or length of follow-up;
- Perioperative complication rate was only 5/245 (2%), with 1 bladder perforation, 1 urethral perforation and 3 vaginal sulcus perforations;
- Vaginal extrusion rate was 8/161 (4.9%) for UraTape and 1/84 (1.2%) for ObTape;
- Urinary retention rate was 2% (5/245) with 2 tape releases required;
- Qmax decreased insignificantly from 31 to 29 ml/s after surgery;
- Urgency improved in 57% of patients; and
- De Novo urgency rate was 8.3 % (10/121).

Krauth et al [19] reported their experience with the transobturator approach using the I-STOP device at six centers. Of 604 patients, 92 % had isolated treatment for stress incontinence. They report a bladder perforation rate of 0.5%, hematoma rate of .16%, transient urinary retention 1.5%, and transient perineal pain 2.3%. Short-term failure rates defined as no improvement were 3.1%. Unfortunately, they do not break down their improved patients into cures and improved and instead cite an 85.5% satisfaction rate.

There are two studies in the literature that compare RMUS and TMUS, one of which is a randomized, prospective trial, that demonstrated equivalent efficacy between the RMUS and TMUS [20, 21]. However, both studies are limited by short follow-up and small sample size. Mansoor reported preliminary results from a RCT comparing TVT with ObTape in an abstract at the ICS in 2002 [20]. The abstract provides data on the first 102 patients enrolled with 6 - 17 month follow-up. They report cure rates for TVT of 93% and TOT 96%. They also reported 5 bladder lacerations in the TVT group and one urethral laceration in the TOT group. There are several shortcomings of these data since they had enrolled only 50% of their sample size, the follow-up was short and details of their study design have not been published. Mellier retrospectively compared two non-randomized groups of women, 94 patients who had undergone TMUS between June 2001 and December 2002 and 99 patients who had undergone TVT procedures between January 1999 and June 2001 [21]. The same mesh sling was used for patients in both groups. They reported a bladder perforation rate of 10% for TVT vs. 0% in the TMUS group. There were no other statistically significant differences in complications. Efficacy rates were similar, although the investigators point out that the length of follow-up was different between the two groups.

De Leval described a modification of the TMUS in 2003 that employed a similar inside-to-outside approach as that employed by TVT, arguing that urethral injuries could be avoided. For 107 patients who underwent this procedure between March 2002 and February 2003, he reported no vaginal, urethral or bladder intra-operative complications, one vaginal erosion at 1 month, and three patients with retention resolved after tape release. He reported 15.9% of patients complained of moderate pain in the thigh folds that resolved within 2 days for all but 2 patients. No efficacy data were reported [22]. At the ICS Meeting in 2005, he presented data from the first 90 patients demonstrating a 90% cure rate and no complications.

A.3 Selection of Minimally Invasive Procedures for Study

Multiple versions of the original RMUS have been developed by a number of companies. Many of these modified the original procedure by using a different mesh material for the sling, a different surgical approach for placement of the sling, or a combination of both. Since the goal of this study is to compare the outcomes and morbidity between two approaches, it is important that all other variables between the two procedures are controlled. Prior to choosing which MUS to perform in each arm, the current literature on the differences between the various MUS products currently approved for use in the United States was reviewed.

Three surgical approaches have been developed for the mid-urethral sling, i.e., the original retropubic, the suprapubic, and the transobturator. The suprapubic approach, first popularized by the SPARC procedure, has not demonstrated any decrease in morbidity nor does it have the theoretical advantage of staying out of the retropubic space. In fact, there are conflicting results in the literature on whether its efficacy equals that of the original RMUS procedure, TVT. The transobturator approach, on the other hand, provides the unique advantage of staying out of the retropubic space and offers the most potential for improving the rare but significant risks associated with the original RMUS procedure. While the early data suggest efficacy is similar to the original RMUS procedure, it comes from case series and non-randomized trials not designed to truly assess the difference between the two procedures.

There are two methods for performing the TMUS procedure based on the direction of the trocar passage, inside-out or outside-in. There is insufficient evidence to recommend one over the other. Potential differences between the two TMUS methods include the size of the vaginal incision, the amount of peri-urethral dissection, and the location of the trocar from the obturator neurovascular bundle as it passes through the obturator foramen. While there are theoretical concerns about the potential effects these differences may have on efficacy and safety of the TMUS procedure, there is no evidence that they are clinically significant. In fact, the data that do exist are from case series studies that would suggest the two methods are similar in both efficacy and safety. A three arm design comparing the inside-out TMUS approach, the outside-in TMUS approach, and the traditional RMUS was considered seriously. However, we do not think that the two TMUS techniques are different enough to justify the increased cost and recruitment time needed for the larger sample size required for a three-arm study design. Therefore, we elected to allow the use of either approach for the TMUS procedure.

A.4 Selection of Mesh Products for Use in Study

The preponderance of published data on midurethral sling procedures is based on the original RMUS procedure described by Ulmsten, the TVT [8-10]. The mesh used in the original TVT is a monofilament, large pore (> 500 microns), single weave polypropylene material. There are currently 6 different MUS products that utilize mesh of this type. Each claims to have some quality that makes it preferable for incontinence surgery. After review of the product specifications and the limited data in the literature, it was clear that no two meshes are identical. Some of the characteristics that differ between products include tensile strength, elongation at break, stiffness, edge treatment, density, and fiber size. It is not known whether any of these characteristics are advantageous or not. Indeed there is a history of new mesh materials being advocated as having the ideal sling characteristics only to find out later that there was some aspect that caused higher complication rates. Since there is little evidence that questions the

efficacy or safety of the TVT type of mesh in the surgical treatment of stress incontinence, this study will standardize mesh material to the same mesh characteristics as the original RMUS procedure, the TVT. After analyzing the product specifications of each mesh and performing tensile strength studies in the biomechanics laboratory at the University of Pittsburgh (unpublished data), the TMUS mesh most similar to the TVT mesh is the mesh used in the TVT-O and Monarc products. Therefore, the products selected for this protocol will be the TVT (Gynecare) in the retropubic arm and either the TVT-O (Gynecare) or the Monarc (AMS) in the transobturator arm. The primary aim of this study is not to compare specific products, but rather to compare two distinct surgical approaches to the mid-urethral sling, the original RMUS and the TMUS.

A.5 Duration of Study

While the investigators understand the importance of long-term follow-up in evaluating the outcomes of surgical treatment of stress incontinence, they also feel strongly that data regarding the immediate safety and short term efficacy of these procedures is urgently needed. Therefore, the proposed primary endpoint is at 12 months so that any observed difference in efficacy for the two procedures can be disseminated. On the other hand, if the efficacy and safety of the two procedures are equivalent, then patients will continue to be followed to assess the longer term outcomes. Patients will be enrolled for 24 months follow-up at the outset and preferably would be followed for 48 months if sufficient resources are available.

A.6 Concomitant Surgical Procedures

There are good arguments to conduct this trial in a population of women who are having isolated incontinence procedures in order to obtain outcome data uncomplicated by the performance of concomitant surgeries. However, the reality is that women undergoing surgery for SUI have a high incidence of concomitant pelvic prolapse. Most studies of RMUS report that between 30-60% of women have a concomitant procedure at the time of their RMUS [23-26]. In the UITN SISTEr trial, 58% of women underwent a concomitant surgical procedure (unpublished data). While concomitant procedures may affect some of the secondary outcomes (e.g., return to voiding, hospital stay, pain and return to activities), including them offers two advantages: 1) the sample will represent the population of women undergoing these procedures and 2) the time required for accrual will be decreased by one-third or more. In an attempt to limit the confounding effect of these procedures, concomitant surgeries for prolapse will be limited to vaginal procedures. Additionally, graft material will not be allowed in the anterior compartment and use of synthetic graft material will not be allowed at all.

A.7 Prognostic Utility of Urodynamic Studies (UDS)

This study also provides an opportunity to evaluate the clinical utility of urodynamics. UDS are commonly performed in the United States as part of the pre-operative evaluation in women being considered for stress incontinence surgery at a cost of upwards of $1000 per patient. However, it is not clear whether the pre-operative utilization of urodynamics data affects outcomes or post-operative management of lower urinary tract dysfunction. The justification for this practice varies greatly between clinicians and includes: 1) excluding mixed incontinence or detrusor overactivity patients from surgery, 2) selecting the type of procedure, 3) enabling the surgeon to make intra-operative modifications of the procedure, and 4) providing a baseline

assessment of voiding function to help manage post-operative complications. The clinical utility of preoperative urodynamic studies is best evaluated in a randomized clinical trial, such as the proposed RMUS vs. TMUS trial. Surgeons will be blinded to results of preoperative UDS throughout the study unless required for treatment of post-operative lower urinary tract dysfunction.

B. Study Aims and Hypotheses

B.1 Primary Aims

- To compare objective cure rates (defined below) for urinary incontinence at 12 and 24 months between RMUS and TMUS.
- To compare subjective cure rates (defined below) for urinary incontinence at 12 and 24 months between RMUS and TMUS.

B.2 Secondary Aims

- To compare the subjective and objective cure rates of stress-specific urinary incontinence between RMUS and TMUS.
- To compare self-reported bother from UI symptoms at 1 and 2 years between RMUS and TMUS.
- To compare time to adequate voiding, patient satisfaction, QOL, and time to resumption of normal activities between the two procedures.
- To compare the morbidity between RMUS and TMUS, including intraoperative injury, voiding dysfunction, *de novo* urge incontinence, and pain.
- To assess efficacy of each procedure in two sub-groups
  - Patients undergoing only the RMUS/TMUS procedures; and
  - Patients undergoing RMUS/TMUS and concomitant prolapse surgery limited to repairs performed vaginally with no use of other graft material.
- To determine the clinical utility of preoperative urodynamic studies.
- To assess long-term efficacy and complications (notably, voiding dysfunction and de novo urge incontinence) of the TMUS and RMUS at 4 years.

B.3 Other Hypotheses

- Return to adequate voiding will be more rapid in patients undergoing the TMUS procedure than in patients undergoing the RMUS procedure.
- Long-term voiding dysfunction will be less common in patients undergoing the TMUS procedure than in patients undergoing the RMUS procedure.
- Patients undergoing the TMUS procedure will report shorter time to return to normal activities than will patients undergoing the RMUS procedure.
- Patients undergoing the TMUS procedure will report less post-operative pain than will patients undergoing the RMUS procedure.
- De novo and persistent urge incontinence will occur less frequently in patients undergoing the TMUS procedure than in patients undergoing the RMUS procedure.

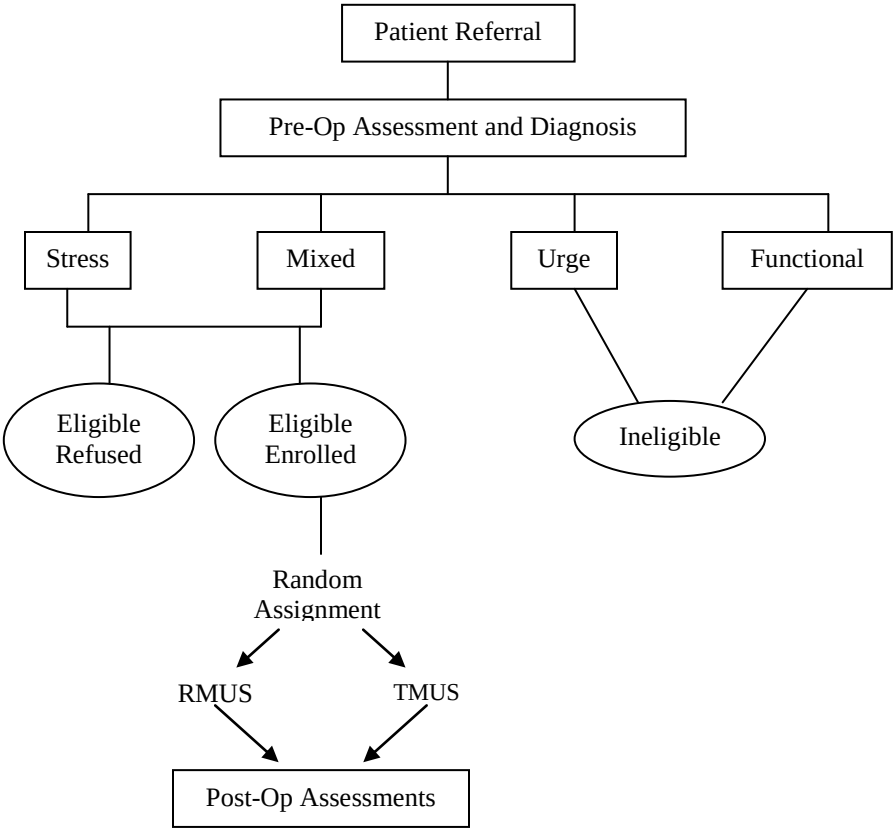
- Poor urethral function as measured by urethral function tests (LPP, MUCP) predicts failure for both procedures.
- Poor urethral function as measured by urethral function tests (LPP, MUCP) is more likely to predict failure for the TMUS procedure than for the RMUS procedure.
- Abnormal preoperative voiding on free uroflowmetry (low Qmax, high PVR, strain pattern or other abnormal pattern) or on the pressure flow study (PFS) (low Qmax, high pdet, voiding mechanism) predicts postoperative voiding dysfunction or postoperative abnormal free uroflowmetry or PFS.
- Post-operative voiding dysfunction defined by the pressure flow study (PFS) will be greater for the RMUS procedure than for the TMUS procedure.
- Measures of urethral function (VLPP and MUCP) do not correlate with each other or with UI severity.

C. Study Design

The fact that surgical trials in incontinence have failed to meet contemporary standards for outcome analysis highlights the difficulty in accomplishing these studies, especially when multicenter trials are needed to ensure adequate statistical power of the study. A randomized clinical trial will provide the best scientific evidence for answering the question of relative efficacy of the RMUS and TMUS procedures. This design will eliminate the confounding factors introduced by strong surgeon and patient preferences, and different patient populations and referral patterns at the different clinical centers. These factors would be very difficult to measure and adjust for in a non-randomized observational treatment comparison.

The design of the trial is depicted in Figure 1.

Figure 1. Trial Design



NOTE: Concomitant surgery for prolapse will be allowed, but limited to vaginal procedures.

D. Definition of Treatment Success

Treatment success for this study will be assessed both objectively (clinically) and subjectively (patient report). The *a priori* primary time point for evaluating success is at 12-months.

Objective treatment success is met if all of the following are met:

- A negative stress test;
- A negative pad test (<15 ml urine leakage over 24 hours); and
- No retreatment for SUI (including anti-incontinence surgery, treatment with a device, periurethral bulking agents, medication, behavioral treatment, etc.).

Subjective treatment success is met if all of the following are met:

- No self-reported leakage by 3-day voiding diary; and
- No self-reported stress-type UI symptoms (MESA questionnaire: response of "rarely" or "never" for each stress-type symptom); and
- No retreatment for SUI (including anti-incontinence surgery, treatment with a device, periurethral bulking agents, medication, behavioral treatment, etc.).

Objective treatment failure is therefore defined by the occurrence of one or more of the following:

- Any surgical, pharmacological, device or behavioral retreatment for SUI at any point after the initial surgery for urine leakage;
- A positive stress test ≥ 3months after surgery; or
- A positive pad test (≥15 ml leakage over 24 hours) ≥ 3months after surgery.

Subjective treatment failure is defined by the occurrence of either or both of the following:

- Self-reported stress-type UI symptoms (response of "sometimes" or "often" on the MESA questionnaire) ≥ 3months after surgery;
- Self-reported leakage by 3-day voiding diary ≥ 3months after surgery; or
- Any surgical, pharmacological, device or behavioral retreatment for SUI at any point after the initial surgery for urine leakage.

Once a woman is documented as a treatment failure, she cannot be classified as a success for that endpoint at later time points.

E. Study Population

The study population will consist of women who have been diagnosed with stress urinary incontinence (SUI).

Inclusion Criteria

1. Female
2. SUI as evidenced by all of the following:
    - Self-reported stress-type UI symptoms, of duration ≥3 months*
    - MESA 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 provocative stress test at a bladder volume ≤300ml
    - Bladder capacity ≥200ml by stress test

- Post-void residual (PVR) ≤100cc with pelvic organ prolapse (POP) Stage I or lower. If POP is Stage II-IV, PVR >100cc but ≤500cc is allowed

3. Eligible for both RMUS and TMUS procedures
    - No medical contraindications, e.g., current UTI, history of pelvic irradiation, history of lower urinary tract cancer
    - ASA class I, II, or III
    - No current intermittent catheterization
4. Available for 24-months of follow-up and able to complete study assessments, per clinician judgment
5. Signed consent form

*Patient can be rescreened after respective time interval has been met.

Exclusion Criteria

1. Age <21 years*
2. Non-ambulatory (ambulatory with assistive devices does not exclude the patient)
3. Pregnancy by self-report or positive pregnancy test, or self-reported intention to ever become pregnant
4. Current chemotherapy or current or history of pelvic radiation therapy
5. Systemic disease known to affect bladder function (i.e., Parkinson's disease, multiple sclerosis, spina bifida, spinal cord injury or trauma)
6. Urethral diverticulum, current or previous (i.e. repaired)
7. Prior augmentation cystoplasty or artificial sphincter
8. Implanted nerve stimulators for urinary symptoms
9. History of synthetic sling for SUI
10. <12 months post-partum*†
11. Laparoscopic or open pelvic surgery, or any other endoscopic or significant pelvic surgery <3 months*
12. Current evaluation or treatment for chronic pelvic pain (painful bladder syndrome)
13. Participation in another treatment intervention trial that might influence the results of this trial
14. Need for any concomitant surgery except for vaginal prolapse repairs that do not require an abdominal incision, or need for any use of graft material in the anterior compartment, or need for any use of synthetic graft material. (NOTE: Minor concomitant diagnostic procedures such as vulvar biopsies, hysteroscopy, D&C will be allowed. Procedures performed strictly for cosmesis will not be allowed.)
15. Enrollment in SISTEr/E-SISTEr or BE-DRI/E-BE-DRI
16. Previous placement of synthetic mesh on a vaginal approach to reconstructive surgery.

*Patient can be rescreened after respective time interval has been met.

†"Partum" is defined as a delivery or other termination that occurs after 20 weeks gestation.

If more than 6 months transpire between determination of eligibility and surgery, specified measures must be repeated before randomization to ensure current eligibility for the trial as well as to obtain current baseline values for critical measures that are subject to change. (See Section H.6 and Appendix A.)

F. Randomization

Patients will be randomized in the operating room to either the RMUS or TMUS procedure. The process of obtaining the randomized treatment assignment will be accomplished by an automated randomization system at the Biostatistical Coordinating Center (New England Research Institutes). A back-up system of randomization using sealed envelopes will be made available in the case of technical problems. Randomization will be stratified by clinical site, using permuted blocks.

G. Treatments

G.1 Operative Procedures

The procedures included in this trial are the retropubic transvaginal midurethral sling (RMUS) and the transobturator midurethral sling (TMUS), including both the inside-to-outside and outside-to-inside TMUS approaches.

G.2 Standardization of Operative Procedures

Recognizing the need for both internal and external validity, the procedures will be standardized across participating surgeons.

G.3 Certification Requirements for Study Surgeons

Surgeons participating in this trial will be certified prior to commencing study operative procedures. Each surgeon will select *a priori* the TMUS procedure (inside-to-outside or outside-to-inside) s/he will use throughout the trial. Certification requirements include completion of at least five of each operative procedure in clinical practice followed by demonstrated compliance in the performance of each procedure per UITN protocol as observed by a UITN PI or Co-PI.

All operative procedures will be performed, or directly supervised, by a UITN certified surgeon. Fellows and residents may participate in the surgery. However, the tensioning portion of the procedures must be performed by the certified surgeon Investigator.

H. Measures

H.1 Primary Outcome Measures

The primary outcome measures for objective treatment success, measured at 12-months, consist of a provocative stress test, 24-hour pad test, and any retreatment for SUI.

The primary outcome measures for subjective treatment success, measured at 12-months, consist of self-reported stress-type UI symptoms using the MESA questionnaire, the 3-day voiding diary, and any retreatment for SUI.

a. Stress Test

A provocative stress test standardized to volume and position will be performed for direct observation of urine leakage [27]. Observed urine loss from the urethra coincidental with the Valsalva maneuver or cough is a positive test.

b. Pad Test

Pad testing is used as a means of quantifying the amount of urine involuntarily lost. The 24-hour pad test will be used to reflect everyday incontinence [28]. The test has been standardized by the International Continence Society (ICS) [29], correlates well with UI symptoms [30], and has good reproducibility [31].

c. Retreatment or Additional Surgery

The need for any additional treatment for SUI at any time after the index procedure will constitute a treatment failure**.** Additional treatment includes additional anti-incontinence surgery, collagen injections or periurethral bulking injections, and medications or behavioral treatments (i.e. behavioral treatment for SUI is defined as a formal structured treatment program, which therefore excludes informal discussion, suggestions and/or handouts) specific to SUI as follows:

Surgery:

- Burch colposuspension
- Sling procedure
- Needle suspension (Raz, Pereyra, Stamey, Gittes, etc.)
- Suburethral plication
- Collagen injections or periurethral bulking agents
  (NB: Surgery for prolapse is not defined as failure of SUI procedure.)
  (NB: Surgical "take down" of a sling is not defined as failure of SUI procedure; rather, "take down" is considered a complication, as is the broader category of voiding dysfunctions requiring treatment.)

Pharmacologic treatment:

- Alpha-agonists
- Duloxetine
  (NB: Estrogen treatment is not defined as failure of SUI procedure.)

Other treatments:

- Pelvic muscle rehabilitation (with or without biofeedback) for the indication of treatment of SUI
  (NB: PMR for treatment of urge incontinence is not defined as failure of SUI procedure.)
- Devices such as vaginal cones, pessary, urethral plugs or patches for SUI
  (NB: Pessary for prolapse is not defined as failure of SUI procedure.)

d. MESA

Self-reported stress-type UI symptoms will be collected using selected items regarding stress and urge-type UI symptoms taken from the questionnaire for the Medical, Epidemiologic, and Social Aspects of Aging Project (MESA) conducted at the University of Michigan [32]. The items query the patient's description of how urine loss occurred. Questions referring to loss of urine at times of exertion such as laughing, sneezing, lifting, or bending over define SUI. Questions referring to urine loss preceded by an urge to void, or uncontrollable voiding with little or no warning define urge incontinence. Symptoms associated with urine loss of both urge and stress-types define "mixed" incontinence. For the purposes of this trial, predominant SUI is defined as the percent of stress-type symptoms > the percent of urge-type symptoms. Agreement between the MESA questions and a clinician's assessment has been reported as 87% for women [32]. The authors further noted that self-reported stress-type symptoms had an accuracy of 69% in predicting a urodynamic diagnosis of SUI.

e. Voiding Diary

Self-monitoring of voiding behavior and frequency using a daily dairy is a practical and reliable method for assessing the frequency of voluntary micturitions and involuntary episodes of urine loss [33-35]. The diary has the advantages of reducing recall error and results in higher levels of reporting for most conditions [36]. Several variations of a urinary diary have been used for clinical and research purposes. Recommended duration for keeping the diary ranges from 3 – 14 days [37, 38]. For purposes of this trial, a 3-day diary will be used, based on the results of reliability testing by Nygaard and Holcomb in women with genuine SUI [34]. They reported a correlation of 0.887 between the first 3 days of a diary and the last 4 days, suggesting that a 3-day diary is an appropriate outcome measure for clinical trials evaluating treatments for SUI.

H.2 Secondary Outcome Measures

a. Quality of Life and Patient Bother

Because no direct relationship has been reported between a patient's level of distress and a patient's level of satisfaction with treatment, it will be important to measure the impact of treatment outcome on the patient's *quality of life* (QOL). Health-related QOL is a multidimensional concept which encompasses well-being that is related to health and is distinguished from measures of health and functional status. Two condition-specific measures will be used in this trial so as to be sensitive enough to detect change, i.e. the International Consultation on Incontinence Questionnaire (ICIQ) [39] and the Incontinence Impact Questionnaire (IIQ) developed by Shumaker et al [40]. The former measure assesses the impact of UI on everyday life whereas the latter measure assesses the impact of UI on various activities, roles, and emotional states. *Patient bother* will be measured by the subscales of the Urogenital Distress Inventory (UDI) measuring stress UI symptoms, urge symptoms and voiding symptoms [34]. Adequate validity, reliability and sensitivity to change have been reported by the authors.

b. Improvement in Frequency of UI Episodes

The 3-day voiding diary, as previously described, will be used to measure frequency of UI episodes at the follow-up time points. The difference between the baseline and follow-up frequency will measure change in frequency.

c. Return to Adequate Voiding

"Adequate voiding" is defined as voiding with a post void residual $\leq$ 100 cc AND $\leq$ 1/3 of the total bladder volume. Voiding function will be evaluated at baseline, early postoperatively in the hospital, and at the 2- and 6-week study visits. Standardized voiding trial procedures will be followed across all centers in order to standardize bladder volume prior to the voiding trial and to obtain the most accurate PVR measurements. The postoperative voiding trial will be performed on the day of surgery (unless other circumstances including the performance of concurrent repair procedures influence a delay of the voiding trial). For patients who fail their post-op voiding trial or require post-op catheter drainage, an interim voiding trial will be conducted 2-4 days post-discharge. Interim voiding trials may be repeated prior to the 2-week visit for patients who still demonstrate inadequate voiding. PVR will be measured at both the 2- and 6-week visits.

In addition to these objective measures, adequate voiding will be evaluated subjectively by the Urogenital Distress Inventory (UDI) [34] and the self-reported voiding questions (i.e. voiding mechanisms, bother with such mechanisms, description of urine stream, time it takes to void) used in the SISTEr study, comparing responses at the 2- and 6-week visits to baseline responses.

d. Pain

Post-op pain will be assessed using a modified version of the 4-item Surgical Pain Scales (SPS) developed by McCarthy et al [41]. Patients will also be asked to identify specific location (anatomical pictures) and rate the intensity of pain they attribute specifically to the TOMUS surgical procedure. Self reports will be completed by all patients pre-operatively, daily for 2-weeks post-operatively, and at every post-op study visit. Patients who complain of surgical pain at the 2-week visit will continue to complete the daily pain diary for an additional 2 weeks. Objective information will also be gathered by examination at baseline and the 2-week and 6-week post op visits. The circumstances under which pain will be considered a complication are described in Section H.2.h.

e. Patient Satisfaction with Treatment Outcome

Due to the increasing concern regarding patient satisfaction with medical care and the documented association between satisfaction and treatment adherence [42], patient satisfaction has been included as a secondary outcome. A 9-item self-administered questionnaire developed for the UITN SISTEr trial will be used to assess this outcome. These items measure patient satisfaction with the result of surgery related to activities previously restricted by UI symptoms and to emotions associated with UI, as well as providing a measure of patients' global sense of satisfaction with the outcome.

In addition, the Patient Global Impression of Severity and Improvement questions (PGI-S and PGI-I) will be administered to gather information regarding women's overall appraisals of their conditions and their responses to treatment [43]. Yalcin et al demonstrated that these questionnaires were correlated significantly with incontinent episode frequency, pad test outcomes and Incontinence Quality of Life Questionnaire measures. A unique benefit provided by these measures is their ability to account for the preferences of individual patients.

f. Resumption of Normal Activities

Patients will be given a standard set of post operative instructions developed specifically for this trial (Appendix B). These instructions will specify time restrictions for identified activities. To assess return to normal activities, the Activities Assessment Scale developed by McCarthy et al [44] will be used. This instrument was developed for use in assessing difficulty in post-operative resumption of daily activities. Adequate validity, reliability, and sensitivity to change have been reported by the authors. In addition, the SISTEr questions regarding number of days to return to normal activities will be included. While noted that normal activities might include work, the number of days to specifically return to work will not be considered as this activity is often determined by the amount of approved medical leave rather than physical recovery from surgery.

g. Sexual Function

Little is known about the sexual functioning of women with UI. As with measurement of QOL, a condition-specific measure of sexual function will be used in this trial. The short form of the Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ) developed by Rogers et al is a 12-item self-administered questionnaire [45]. Adequate validity, reliability, and sensitivity to

change have been reported by the authors [46]. A Spanish version of the PISQ-12 has been validated [47] and will be used in this trial.

h. Complications and Morbidity

Complication is defined as any adverse deviation from the normal intraoperative or postoperative course. As indicated, the severity of complications will be graded using the validated system of Dindo et al [48] modified slightly for use in this study (See Appendix C). Any complication reported as "other" will be reviewed by the TOMUS Complications Committee and coded according to the System Categories in Appendix C.

The following intraoperative and postoperative complications of the mid-urethral sling procedures, including their operational definitions, will be reported.

- Bladder Perforation: Unplanned piercing made through the bladder, recognized intraoperatively.
- Urethral Perforation: Unplanned piercing or creation of an opening in the urethra, recognized intraoperatively.
- Acute Renal Failure: As diagnosed by a nephrology consult. 6 week reporting limit.
- Anesthetic Complication 6 week reporting limit.
- Deep Venous Thrombosis: Initiation of anticoagulation therapy for a thromboembolic event. 6 week reporting limit.
- Pulmonary Embolus: Diagnosed within 6 weeks of surgery or at any time secondary to a DVT that was diagnosed within 6 weeks of surgery.
- Myocardial Infarction: Documented by ECG changes or elevation of cardiac enzymes, as confirmed by cardiology consult, within 6 weeks of surgery.
- Cerebrovascular Accident: Documented by CT scan or neurologic consultation within 6 weeks after surgery.
- Death: 6 week reporting limit.
- Bleeding: Intraoperative: pelvic and obturator vessels, abdominal wall; Estimated blood loss (EBL) greater than 100 cc attributable to the placement of the midurethral sling OR estimated blood loss for the total case greater than or equal to 1000 cc and/or requiring intraoperative blood transfusion.

  Postoperative: pelvis, thigh, vagina, abdominal wall; Bleeding from a wound or from a contained space that resulted in intervention. 6 week reporting limit.
- Bowel Injury: Confirmation of injury to small or large bowel by laparotomy or imaging studies. 6 week reporting limit.
- Rectal Injury: Perforation of the rectum. 6 week reporting limit.
- Vascular Injury: Injury to a major blood vessel, diagnosed by imaging study or surgical intervention. 6 week reporting limit.
- Device Malfunction: Any abnormal occurrence attributable specifically to the sling device during placement, i.e. trocar releases from sling material, abnormality of the protective sleeve surrounding the sling material, etc. Recognized intraoperatively.
- Mesh Complication: Vaginal, urethral, bladder; erosion (defined as after primary healing, into an organ or surrounding tissue); exposure (defined as mesh visualized through a prior incision area with or without an inflammatory reaction). No time limit for reporting.

- Surgical Site Infection (based on 1992 CDC definition): No time limit for reporting. One of the following criteria must be met:
    - Evidence of any of the following signs at the surgical incision site: purulent drainage, pain or tenderness, localized swelling, redness or heat.
    - Deliberate opening of the wound unless culture negative.
    - Evidence of infection on re-operation or imaging study.
    - Diagnosis of infection by physician, confirmed by study surgeon.

  Surgical site infections will be subcategorized into the following types:
    1. Superficial Incisional: Involves only the skin and subcutaneous tissues at the incision site(s).
    2. Deep Incisional: Involves deep soft tissue (e.g. fascial and muscle layers) at the operative site(s).
    3. Organ/space: Organs or spaces, other than the incision, that were opened or manipulated during the operative procedure (includes pelvic abscess, peritonitis).
- UTI - Empiric: Prior to 6-weeks, patient receives antibiotic therapy for symptoms thought to be secondary to UTI. 6 week reporting limit.
- UTI - Culture-Proven: Prior to 6-weeks,patient receives antibiotic therapy for symptoms of urinary tract infection subsequently associated with a positive culture. 6 week reporting limit.
- Recurrent UTI: Presumed UTI with treatment, ≥3 in 1 year AFTER 6 week visit. No time limit for reporting.
- Fistula: No time limit for reporting.
    - Vesicovaginal: connection between bladder and vagina resulting in passage of urine per vaginum
    - Urethrovaginal: connection between urethra and vagina resulting in passage of urine per vaginum
    - Enterovesical: connection between bladder and bowel, may be diagnosed by pneumaturia, charcoal study, or cystoscopy
    - Rectovaginal: connection between the rectum and the vagina resulting in the passage of stool per vaginum.

  NOTE: Foreign body reaction in space of Retzius resulting in vaginal discharge or bleeding or granulation tissue in vagina is NOT a fistula.
- Neurologic Symptoms: 6 week reporting limit.
    - New paresthesias or alteration in motor function that develop between surgery and the 6 week visit. Will be considered a neurological complication related to surgery if the patient answers "yes" to either of following two questions (questions will be asked at baseline, 2-week and 6-week visits):

      1. Do you have any numbness in your legs or pelvic area that has developed since surgery? If yes, describe location and magnitude.

          a. Location: Patient to mark body map. Body map will have areas labeled that correspond to the following data points.

              - Suprapubic
              - Groin
              - Vulva
              - Upper leg

- Lower leg

b. Magnitude: Measured by answering the following question: "How bothersome is the numbness that you described and relate to your surgery?" Response categories are: *not at all bothersome, slightly bothersome, moderately bothersome* and *greatly bothersome*.

2. Do you have any weakness in your legs or pelvic area that has developed since surgery? If yes, questions noted above will be used to get information about location and magnitude.

- Granulation Tissue: At or beyond the 6 week visit, granulation at the TOMUS surgical site. (If at or beyond 6 weeks there is granulation at a concomitant surgery site, that should be reported as an "other" [code 99] adverse event.) No time limit for reporting.
- Pain (no time limit for reporting): Defined as a complication if the following criteria are met at or beyond the 6 week visit:
    1. Patient answers "yes" to the introductory stem question "Have you had any pain within the last 24 hours as a result of your incontinence operation?" AND
    2. Patient answers any of the first three McCarthy pain questions at a level 75mm or greater on the visual analog scale (150mm total length). AND
    3. Patient answers the bother question on the McCarthy visual analog scale at a level 75mm or greater.
- Voiding Dysfunction (no time limit for reporting): Defined as a complication if one of the following criteria are met:
    - Uses a catheter to facilitate bladder emptying at or beyond the 6 week visit OR
    - Has undergone medical therapy to facilitate bladder emptying at or beyond the 6 week visit OR
    - Has undergone surgical therapy to facilitate bladder emptying at anytime after TOMUS surgery.
- De Novo Urge Incontinence (no time limit for reporting): - At or beyond the 6-week visit, in the absence of a positive urine dipstick, a baseline pure SUI patient now answers.
    1. Any MESA urge question "sometimes" or "often," AND/OR,
    2. Has initiated treatment with anticholinergic medication for urge incontinence.
- Persistent Urge Incontinence (will be tracked, but not reported as a complication.) At or beyond the 6 week visit a baseline mixed patient answers,
    1. Any MESA urge question "sometimes" or "often," AND/OR,
    2. Has initiated treatment with anticholinergic medication for urge incontinence

  NOTE:
    - Baseline status definitions for urge incontinence are as follows:
        - Pure SUI
            1. All MESA urge questions are answered "never" or "rarely," AND,
            2. Patient is not being treated with anticholinergic medication for urge incontinence.
        - Mixed SUI
            1. Any MESA urge question is answered "sometimes" or "always," AND/OR,
            2. Patient is being treated with anticholinergic medication for urge incontinence.

i. Post-Operative Treatment of Lower Urinary Tract Symptoms

Post-operative treatment of lower urinary tract symptoms will be allowed as follows:

- Medications can be prescribed for overactive bladder, incontinence or voiding dysfunction no sooner than 2-weeks post-op.
- Surgical treatment for urinary retention can be performed no sooner than 2-weeks post-op.
- Surgical treatment for elevated PVR or urgency/frequency symptoms can be performed no sooner than 6-weeks post-op.

j. Urodynamic Studies

Urodynamics, using a standardized UDS protocol, will be conducted baseline and post-operatively at 12 months or at baseline and prior to surgical retreatment for SUI. UDS must also be conducted prior to any surgery for lower urinary tract dysfunction. The protocol for this study was modified from that used in the SISTEr study to:

1) include measure of maximum urethral closure pressure (MUCP);
2) exclude EMG; and
3) for patients with Stage III or IV anterior pelvic organ prolapse, cystometry will be performed without reduction of the prolapse.

UDS studies will be performed by a certified UDS tester and interpreted by a co-investigator at the local site who is not the surgeon. The surgeon will be blinded to the preoperative UDS results throughout the trial unless required for treatment of post-operative voiding dysfunction. A surgeon cannot perform the TOMUS surgery for a given patient if s/he reviewed or interpreted a UDS within the last 6 months for that patient.

The UDS tracing will be sent to a central repository. Post-operative analysis of UDS data will be performed to assess whether certain UDS variables are predictive of clinical outcomes. Results will not be used for eligibility determination, as the surgeon will be blinded to these data. Additionally, post-operative assessment of lower urinary tract dysfunction will be completed without use of preoperative UDS information. Once the diagnosis and treatment plan for the post-operative lower urinary tract dysfunction have been determined, the pre-operative UDS information will be made available for the clinician to utilize. Changes in the treatment plan after review of the UDS data will be documented in order to assess clinical utility of pre-operative UDS data in post-operative management decisions.

Post-operative UDS data will be used to assess changes in lower urinary tract function secondary to the surgical procedures as well as to correlate with patient symptoms of voiding dysfunction, de novo urge symptoms and persistent urinary incontinence.

k. Costs

Incontinence Expenses Participants will record numbers of pads, protection, laundry, dry cleaning, personal hygiene products, household protection, and household cleaning products consumed specifically for their incontinence. They will also record indirect resources related to incontinence (time spent on incontinence-related healthcare, limits on employment or volunteer work due to incontinence). The Incontinence Expense questionnaire was derived from other published expense surveys and has been validated in a study of over 300 women with incontinence (analyses in progress) [49], [50]. The average national cost of each product will be determined by a survey of several retail and wholesale stores.

Medical Care Utilization Medication use will be determined from the trial and cost will be estimated using the minimum average wholesale price of commonly prescribed medications [51]. Marginal use of resources (provider visits) will be estimated for each treatment group. Direct costs will be calculated using a proxy for societal cost, Medicare resource-based relative value scale charges for physician services [52].

Utilities Patient preferences (also called utilities for states of health) associated with urinary incontinence will be measured with the Health Utilities Index Mark 3 (HUI3). This measure provides a rapid and reproducible quantification of utilities for health states [53], [54]. The HUI3 is a generic health status and health-related quality of life (HRQL) measure based on standard gamble theory that is well tested both in clinical and population health studies. The HUI3 has fifteen multiple choice questions or attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) with five to six severity levels per attribute, ranging from highly impaired to normal. These categorical data on health status can be translated into a utility score that reflects global HRQL [54].

Willingness to pay for Incontinence Improvement Willingness to pay for improvement in incontinence severity reflects the value an individual places on a specific health state by estimating the maximum dollar amount she would pay for health-improving interventions. We will ask women to place a monetary value on both improvement in and cure of incontinence. We will also quantify willingness to pay as a proportion of yearly income. This instrument was designed for the SISTEr study and is based on previous work in urinary incontinence [55].

H.3 Independent Variables

There are three groups of independent variables:

- Sociodemographic characteristics race; marital status; education; occupation;
- Risk factors for UI: age [56, 57]; parity [58-63]; weight of largest baby; menopause status and use of HRT [60, 64]; BMI [63-66]; previous anti-incontinence and gynecologic surgery [56, 60]; current medications [67];
- Type and severity of UI measured by the following: Q-Tip Test; 3-day Voiding Diary.

H.4 Intervening Variables

Intervening variables that might affect the outcomes of interest consist of the following four categories:

- Pelvic comorbidity: pelvic organ prolapse (POP-Q quantification);
- Pre-operative urodynamic values;
- Intraoperative considerations: surgical and medical complications; length of procedure; estimated blood loss;
- Postoperative considerations: length of hospital stay; post-operative pain; time to return to adequate voiding; urinary retention; de novo or persistent urinary urgency or urge incontinence; voiding dysfunction; time to return to normal activities; medical complications;

- Patient expectations of surgery, measured by a 9-item questionnaire developed for the UITN SISTEr trial;
- Depression, measured by the PHQ-9 [68], the depression module of the PRIME-MD diagnostic instrument for common mental disorders.

H.5 Physical Exam and History

The following data will be collected from the pre-operative history and physical examination.

a. History:

- age
- race
- pregnancies (parity, weight of largest baby, number of vaginal deliveries)
- past pelvic surgeries
- history of estrogen replacement therapy
- duration of incontinence
- smoking history
- occupational history
- past surgical and medical incontinence treatments
- frequent UTIs, defined as >3 in previous 12 months
- bowel function, including fecal incontinence

b. Examination:

- height and weight (for BMI); these data will also be collected at 12 and 24-months follow-up
- directed neurological exam: to be recorded as present/absent OR normal/decreased:
    - deep tendon reflex knee
    - perineal sensation
    - anal sphincter voluntary contractions
- strength of pubococcygeus muscle (9-point scale based on strength, duration and movement observed with muscle contraction [69])

c. Q-Tip Test

The Q-Tip Test [70] will be used to quantify bladder neck mobility using a standardized procedure as described in the Physical Examination Procedures Manual.

d. Pelvic Organ Prolapse Quantification (POP-Q)

The pelvic organ prolapse evaluation will be performed according to the guidelines established by the International Continence Society [71]. The procedure will be standardized as demonstrated in a videotape produced by Duke University Medical Center ("Pelvic Organ Prolapse Quantification Examination") and described in the Physical Examination Procedures Manual. In addition to being done at baseline, this measure will also be done at the 12 and 24-month follow-up visits.

H.6 Schedule of Measurements

Data will be collected at baseline, the operative event, 2-weeks, 6-weeks, 6-months, 12-months, and 24 months post-op. The schedule of measurements is displayed in Appendix A.

NOTE: A clean catch urine dipstick will be conducted prior to every visit to ensure patients are infection free and that therefore the data collected are accurate. The decision algorithm based on dipstick results is as follows:

1 Clean catch urine dipstick negative (trace or less) leukocytes AND nitrites - proceed with visit.
2 Clean catch urine dipstick positive (>trace) leukocytes OR nitrites - obtain cath specimen and repeat urine dipstick.
   a. Catheter urine dipstick negative for leukocytes and nitrites - proceed with visit
   b. Catheter urine dipstick positive - send for culture (+/- empiric rx) and reschedule visit within 1 week. Record PVR.

For those patients determined to be a treatment failure because of surgical retreatment for SUI, the 12-month assessment battery will be completed at the time that this surgical retreatment is determined necessary (i.e. before the surgical retreatment). Follow-up visits will continue as scheduled with one exception to the assessment battery at 12 months, i.e. UDS will not be required at 12-months as testing will have been conducted prior to surgical retreatment. If a patient is a treatment failure for any other reason and is going to either forego retreatment OR be retreated with medication and/or behavioral therapy, the 12-month battery, excluding UDS, should be conducted at the time of failure and before any retreatment is initiated. Follow-up visits will continue as scheduled. If the out-of-sequence 12-month assessment is performed within the specified window for the next assessment, then that next assessment can be omitted.

If more than 6 months transpire between determination of eligibility and surgery, all baseline measures except for UDS, the Stress Test and the Q-Tip Test must be repeated before randomization to ensure current eligibility for the trial as well as to obtain current baseline values for critical measures that would be subject to change over a 6-month period. Baseline UDS, Stress Test and Q-Tip Test data expire if they were collected ≥ 12 months prior to surgery. Again, expired measures must be repeated prior to randomization.

I. Statistical Considerations

I.1 Sample Size Determination for Primary Endpoints

The primary endpoint on which the study is powered is "objective treatment success" defined as a negative stress test, a negative pad test and no retreatment for SUI. The primary time point for evaluating success is at 12-months. Although these measures of success cannot be fully documented until 12-months, a failure can be documented earlier (if, for example, a patient requires retreatment at anytime or has a positive stress test ≥3 months after surgery).

We propose to randomly assign 294 women to each treatment condition. The following table provides the maximum allowable difference between cure rates (range of equivalence) for two samples of 250 at 5% significance and 80% power at three levels of underlying cure rates. Prior studies report 24-month cure rates of approximately 60 - 70% and 12-month cure rates as high as 90%. If the two procedures have the same underlying cure rate, samples of 250 participants in each group achieve 80% power at a 5% significance level using a two-sided equivalence test of proportions. The range of equivalence is the maximum allowable difference between these proportions that still results in equivalence.

Common cure rate	Range of equivalence
70%	12 percentage points
80%	11 percentage points
90%	8 percentage points

For subgroup analyses, we will compare cure rates within strata defined by whether the participant had any concomitant surgery or not. We anticipate that approximately half the patients will have concomitant surgery, resulting in samples of 80 patients with each treatment in the two sub-groups. In these sub-group analyses, the range of equivalence is approximately 6 percentage points greater at each cure rate for the same significance and power.

In the UITN SISTEr study, we have follow-up rates of about 85% at 12months and 80% at 24 months. Therefore, to adjust for a 20% loss to follow-up rate, the target sample size will be inflated to 294 per group, or a total sample size of 588 patients.

I.2 Interim Monitoring

Ordinarily, early stopping rules are based on monitoring the primary endpoints for a treatment difference so large that it is unethical to continue treating one group of patients with the "inferior" treatment, and on monitoring the treatments for safety. In this trial, however, several considerations argue against the usual motivations for early stopping procedures.

First, we expect very little primary endpoint data to be available while any participants are still at risk for exposure to either surgery being evaluated. Accrual is expected to take 24 months and success on the primary endpoints is not documented until 12-months after surgery. Therefore, at the time the first participants are reaching the assessment time for documenting "success," approximately one-half of all patients will already have had their surgery. Nevertheless, there will be some information on the primary endpoints prior to 12 months, since retreatment for SUI at any time after the initial surgery will be considered a failure.

Second, both the RMUS and TMUS are surgical procedures in current clinical use. Unlike a trial evaluating an experimental surgical procedure, the study procedures in this trial have documented complications. Because the TMUS is a relatively new approach, it is possible that we will experience some new or unexpected complications. The most common complications of these procedures are urinary tract infections and voiding disorders that can be addressed by release of the tape or intermittent self-catheterization. Rates of the more serious surgical complications (e.g. organ damage, sling erosion, wound infection) will be summarized separately within each site and further within each surgeon, to monitor for problems with specific hospitals or surgeons.

Formal interim data monitoring will be based on a time-to-event analysis, specifically a logrank test, with the event defined as failure of the primary endpoint, as previously defined. With an anticipated 70-90% success rate, we expect about 20% of patients to "fail," or about 100 failures. Formal interim hypothesis testing will be performed after approximately 50 failures have occurred. The methodology of Lan and DeMets will be used to implement an O'Brien-Fleming stopping boundary for this monitoring. The Lan and DeMets methodology allows

flexibility in the exact timing of the interim analyses, so that for example a DSMB meeting can be scheduled for when approximately 50 failures are expected to have occurred. However, if the actual count is not exactly 50, the stopping boundary can be adjusted accordingly. The O'Brien-Fleming boundary is probably the most commonly used stopping boundary because it is conservative early in the trial (i.e. a very strong treatment difference is required for stopping) but maintains close to the nominal significance level toward the end of the trial (i.e. almost any p-value less than .05 at the end of the trial can be considered "significant").

Any early stopping boundary should be considered a guideline and not a hard-and-fast rule. Instead, the evidence should be considered in the context of other study data. Accordingly, DSMB reports will ordinarily include summaries of a variety of endpoints, patient characteristics, adverse events and complications, data quality, and any unanticipated problems that arise during the conduct of the trial.

I.3 Analytic Approach

We will compute the percent of women in each treatment condition who meet the objective and subjective definitions of success at 12 and 24 months post treatment in each treatment arm, RMUS and TMUS. We will use the normal approximation to the binomial distribution to test the equivalence of the two percentages at each follow-up time point. The difference in percent success with 95% confidence limits will provide the estimate of effect Time-to-failure analyses (Kaplan-Meier plots and logrank tests) will also be used in secondary analyses of the two primary outcomes as described above in "Interim Monitoring." Treatment comparisons will be adjusted for covariates with the logistic model for dichotomous endpoints and proportional hazards models for time-to-failure analyses. Analysis of continuous outcomes such as the quality of life 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.

J. Patient Safety

Adverse events (AEs) will be reported in accordance with the Department of Health and Human Services (DHHS) code of federal regulations (Title 45, Part 46). As required, a Data and Safety Monitoring Board (DSMB) will be organized and a meeting schedule established.

References

1. Nilsson, C.G., *Introduction of a new surgical procedure for treatment of female urinary incontinence.* Acta Obstet Gynecol Scand, 2004. **83**(10): p. 877-80.
2. Lose, G. and D.R. Ostergard, *Medical technology assessment and surgery for stress incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 1999. **10**(6): p. 351-2.
3. Vuori, H.V., *Quality assurance of health services*. Public health in Europe. Vol. 16. 1982: Copenhagen: WHO Regional Office for Europe.
4. Nygaard, I.E. and M. Heit, *Stress urinary incontinence.* Obstet Gynecol, 2004. **104**(3): p. 607-20.
5. Boyles, S.H., Edwards, R., *Incidence of complications after trans-obturator sling procedures*, in *31st Annual Society of Gynecologic Surgeons Meeting*. 2005: Rancho Mirage, California.
6. Nilsson, C.G., et al., *Long-term results of the tension-free vaginal tape (TVT) procedure for surgical treatment of female stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2001. **12 Suppl 2**: p. S5-8.
7. Iskander, M.N., D.S. Kapoor, and A. Mohammed, *Subjective outcomes of the TVT procedure.* Int J Gynaecol Obstet, 2003. **83**(1): p. 69-70.
8. Ulmsten, U., et al., *A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 1998. **9**(4): p. 210-3.
9. Ulmsten, U., P. Johnson, and M. Rezapour, *A three-year follow up of tension free vaginal tape for surgical treatment of female stress urinary incontinence.* Br J Obstet Gynaecol, 1999. **106**(4): p. 345-50.
10. Ulmsten, U., et al., *An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 1996. **7**(2): p. 81-5; discussion 85-6.
11. Ward, K.L. and P. Hilton, *A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up.* Am J Obstet Gynecol, 2004. **190**(2): p. 324-31.
12. Paraiso, M.F., et al., *Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial.* Obstet Gynecol, 2004. **104**(6): p. 1249-58.
13. Valpas, A., et al., *Tension-free vaginal tape and laparoscopic mesh colposuspension for stress urinary incontinence.* Obstet Gynecol, 2004. **104**(1): p. 42-9.
14. Deval, B., et al., *A French multicenter clinical trial of SPARC for stress urinary incontinence.* Eur Urol, 2003. **44**(2): p. 254-8; discussion 258-9.
15. Tseng, L.H., et al., *Randomized comparison of the suprapubic arc sling procedure vs tension-free vaginal taping for stress incontinent women.* Int Urogynecol J Pelvic Floor Dysfunct, 2004.
16. Delorme, E., *[Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women]*. Prog Urol, 2001. **11**(6): p. 1306-13.
17. Delorme, E., et al., *Transobturator tape (Uratape): a new minimally-invasive procedure to treat female urinary incontinence.* Eur Urol, 2004. **45**(2): p. 203-7.
18. Costa, P., et al., *Surgical treatment of female stress urinary incontinence with a trans-obturator-tape (T.O.T.) Uratape: short term results of a prospective multicentric study.* Eur Urol, 2004. **46**(1): p. 102-6; discussion 106-7.

19. Krauth, J.S., et al., *Sub-urethral tape treatment of female urinary incontinence--morbidity assessment of the trans-obturator route and a new tape (I-STOP): a multi-centre experiment involving 604 cases.* Eur Urol, 2005. **47**(1): p. 102-6; discussion 106-7.
20. Mansoor, A., Vedrine, N., Darcq, C. *Surgery of female urinary incontinence using trans-obturator tape (TOT): A prospective randomised comparative study with TVT. Abstract #88*. in *ICS*. 2002.
21. Mellier, G., et al., *Suburethral tape via the obturator route: is the TOT a simplification of the TVT?* Int Urogynecol J Pelvic Floor Dysfunct, 2004. **15**(4): p. 227-32.
22. de Leval, J., *Novel surgical technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out.* Eur Urol, 2003. **44**(6): p. 724-30.
23. Rafii, A., et al., *Tension-free vaginal tape and associated procedures: a case control study.* Eur Urol, 2004. **45**(3): p. 356-61.
24. Ng, C.S., R.R. Rackley, and R.A. Appell, *Incidence of concomitant procedures for pelvic organ prolapse and reconstruction in women who undergo surgery for stress urinary incontinence.* Urology, 2001. **57**(5): p. 911-3.
25. Lo, T.S., *Tension-free vaginal tape procedures in women with stress urinary incontinence with and without co-existing genital prolapse.* Curr Opin Obstet Gynecol, 2004. **16**(5): p. 399-404.
26. Darai, E., et al., *Results of tension-free vaginal tape in patients with or without vaginal hysterectomy.* Eur J Obstet Gynecol Reprod Biol, 2002. **103**(2): p. 163-7.
27. Shull, B.L., Halaska, M., Hurt, G., Kinn, A., Laycock, J., Palmtag, H., Reilly, N., Yong Yang & Zubieta, R., *Physical Examination*, in *Incontinence: Proceedings of the 1st International Consultation on Incontinence - June 28-July 1, 1998 - Monaco*, P. Abrams, Saad, K. & Wein, A., Editor. 1999, Health Publications Ltd.: St. Helier, England.
28. Jorgensen, L., G. Lose, and J.T. Andersen, *One-hour pad-weighing test for objective assessment of female urinary incontinence.* Obstet Gynecol, 1987. **69**(1): p. 39-42.
29. Abrams, P., et al., *The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology.* Scand J Urol Nephrol Suppl, 1988. **114**: p. 5-19.
30. Lose, G., Versi, E., *Pad-weighing tests in the diagnosis and quantification of incontinence.* International Urogynecology, 1992. **3**: p. 324.
31. Jorgensen, L., Steen, A., Bagger, P.V., Fisher-Rasmussen, W. *The one-hour pad-weighing test for assessment of the result of female incontinence surgery.* in *15th Annual Meeting of the ICS*. 1985. London.
32. Herzog, A.R., et al., *Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults.* J Gerontol, 1990. **45**(2): p. M67-74.
33. Locher, J.L., et al., *Reliability assessment of the bladder diary for urinary incontinence in older women.* J Gerontol A Biol Sci Med Sci, 2001. **56**(1): p. M32-5.
34. Nygaard, I. and R. Holcomb, *Reproducibility of the seven-day voiding diary in women with stress urinary incontinence.* Int Urogynecol J Pelvic Floor Dysfunct, 2000. **11**(1): p. 15-7.
35. Wyman, J.F., et al., *The urinary diary in evaluation of incontinent women: a test-retest analysis.* Obstet Gynecol, 1988. **71**(6 Pt 1): p. 812-7.
36. Verbugge, L., *Health diaries.* Medical Care, 1980. **18**: p. 73-95.
37. Burton, J.R., *Managing urinary incontinence--a common geriatric problem.* Geriatrics, 1984. **39**(10): p. 46-51, 54, 59 passim.

38. Robb, S.S., *Urinary incontinence verification in elderly men.* Nurs Res, 1985. **34**(5): p. 278-82.
39. Avery, K., et al., *ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence.* Neurourol Urodyn, 2004. **23**(4): p. 322-30.
40. Shumaker, S.A., et al., *Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group.* Qual Life Res, 1994. **3**(5): p. 291-306.
41. McCarthy, M., et al., *Visual Analog Scales for Assessing Surgical Pain.* J Am Coll Surg, 2005. **201**: p. 245-252.
42. Lochman, J.E., *Factors related to patients' satisfaction with their medical care.* J Community Health, 1983. **9**(2): p. 91-109.
43. Yalcin, I. and R.C. Bump, *Validation of two global impression questionnaires for incontinence.* Am J Obstet Gynecol, 2003. **189**(1): p. 98-101.
44. McCarthy, M., et al., *Assessment of Patient Functional Status after Surgery.* J Am Coll Surg, 2005. **201**: p. 171-178.
45. Rogers, R.G., et al., *A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse.* Am J Obstet Gynecol, 2001. **184**(4): p. 552-8.
46. Rogers, R., Qualls, C., Kammerer-Doak, D. & Coates, K., *Short form to assess sexual function in women with urinary incontinence and/or pelvic organ prolapse: the PISQ-11*. International Urogynecology Journal and Pelvic Floor Dysfunction, 2001 b. **12**(Suppl 1): p. S2.
47. Romero, A.A., et al., *Validation of a Spanish version of the Pelvic Organ Prolapse Incontinence Sexual Questionnaire.* Obstet Gynecol, 2003. **102**(5 Pt 1): p. 1000-5.
48. Dindo, D., N. Demartines, and P.A. Clavien, *Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.* Ann Surg, 2004. **240**(2): p. 205-13.
49. Fanti, J.A., Urinary Incontinence in Adults Guideline Update Panel., and United States. Agency for Health Care Policy and Research., *Urinary incontinence in adults: acute and chronic management*. 1996 update. ed. Clinical practice guideline. Acute and chronic incontinence. 1996, Rockville, Md.

Washington, DC: U.S. Dept. of Health and Human Services Public Health Service Agency for Health Care Policy and Research;

For sale by the U.S. G.P.O. vii, 154.

50. Dowell, C.J., et al., *Calculating the direct costs of urinary incontinence: a new test instrument.* BJU Int, 1999. **83**(6): p. 596-606.
51. Cardinale, V., *Drug Topics: Red Book*. 1997, Montvale, NJ: Medical Economics Co, Inc.
52. Health Care Consultants of America, I., *2000 Physicians Fee & Coding Guide*. 2000, Augusta, GA: HealthCare Consultants of America, Inc.
53. Feeny, D., et al., *Multi-attribute health status classification systems. Health Utilities Index.* Pharmacoeconomics, 1995. **7**(6): p. 490-502.
54. Furlong, W., *Multiplicative multi-attribute utility function for the health utilities index mark 3 (HU13) system: a technical report.* 1998: McMaster University Centre for Health Economics and Policy Analysis.
55. Kobelt, G., *Economic considerations and outcome measurement in urge incontinence.* Urology, 1997. **50**(6A Suppl): p. 100-7; discussion 108-10.

56. Milsom, I., et al., *The influence of age, parity, oral contraception, hysterectomy and menopause on the prevalence of urinary incontinence in women.* J Urol, 1993. **149**(6): p. 1459-62.
57. Yarnell, J.W., et al., *The prevalence and severity of urinary incontinence in women.* J Epidemiol Community Health, 1981. **35**(1): p. 71-4.
58. Burgio, K.L., et al., *Urinary incontinence during pregnancy in a racially mixed sample: characteristics and predisposing factors.* Int Urogynecol J Pelvic Floor Dysfunct, 1996. **7**(2): p. 69-73.
59. Foldspang, A., et al., *Parity as a correlate of adult female urinary incontinence prevalence.* J Epidemiol Community Health, 1992. **46**(6): p. 595-600.
60. Jolleys, J.V., *Reported prevalence of urinary incontinence in women in a general practice.* Br Med J (Clin Res Ed), 1988. **296**(6632): p. 1300-2.
61. Sommer, P., et al., *Voiding patterns and prevalence of incontinence in women. A questionnaire survey.* Br J Urol, 1990. **66**(1): p. 12-5.
62. Thomas, T.M., et al., *Prevalence of urinary incontinence.* Br Med J, 1980. **281**(6250): p. 1243-5.
63. Yarnell, J.W., et al., *Factors associated with urinary incontinence in women.* J Epidemiol Community Health, 1982. **36**(1): p. 58-63.
64. Burgio, K.L., K.A. Matthews, and B.T. Engel, *Prevalence, incidence and correlates of urinary incontinence in healthy, middle-aged women.* J Urol, 1991. **146**(5): p. 1255-9.
65. Brown, J.S., et al., *Urinary incontinence in older women: who is at risk? Study of Osteoporotic Fractures Research Group.* Obstet Gynecol, 1996. **87**(5 Pt 1): p. 715-21.
66. Mommsen, S. and A. Foldspang, *Body mass index and adult female urinary incontinence.* World J Urol, 1994. **12**(6): p. 319-22.
67. Montella, A.J., Wordell, C.J., *The effects of drugs on the lower urinary tract.*, in *Urogynecology and urodynamics*, D. Ostergard, Bent, A., Editor. 1996, Williams and Wilkins: Baltimore.
68. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* J Gen Intern Med, 2001. **16**(9): p. 606-13.
69. Brink, C.A., et al., *A digital test for pelvic muscle strength in women with urinary incontinence.* Nurs Res, 1994. **43**(6): p. 352-6.
70. Crystle, C.D., L.S. Charme, and W.E. Copeland, *Q-tip test in stress urinary incontinence.* Obstet Gynecol, 1971. **38**(2): p. 313-5.
71. Bump, R.C., et al., *The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction.* Am J Obstet Gynecol, 1996. **175**(1): p. 10-7.

Appendix A. Schedule of Measurements

	BL (pre-op)	Op	2wk*	6wk*	6m	12m†	24m
Primary Outcomes							
Stress Test	✓***				✓	✓	✓
Pad Test	✓**				✓	✓	✓
New Interventions or Re-treatment			✓	✓	✓	✓	✓
MESA	✓**			✓	✓	✓	✓
Voiding Diary	✓**				✓	✓	✓
Secondary Outcomes							
QOL	✓**				✓	✓	✓
Patient Bother	✓**		✓	✓	✓	✓	✓
Voiding Function: PVR	✓***	✓	✓	✓	✓	✓	✓
Self-report	✓**		✓	✓	✓	✓	✓
Pain: Self-report‡	✓**	✓	✓	✓	✓	✓	✓
Exam	✓**		✓§	✓§			
Patient Satisfaction					✓	✓	✓
Resumption of Activities	✓**		✓	✓	✓		
Sexual Function	✓**				✓	✓	✓
Complications / Morbidity		✓	✓	✓	✓	✓	✓
UDS	✓***					✓	
Urine Dipstick	✓**		✓	✓	✓	✓	✓
Cost Measures	✓**					✓	✓
Independent Variables							
Sociodemographic	✓						
H&P	✓**				✓	✓	✓
Q-tip test	✓***						
Medication Audit	✓**		✓	✓	✓	✓	✓
Intervening Variables							
POP-Q	✓**					✓	✓
Operative Measures		✓					
Depression	✓**				✓	✓	✓
Patient Expectations	✓**						

* Visit frequency between 2-6 weeks will depend on voiding function.

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

*** Measure must be repeated if patient is not randomized within 12 months of completion.

† Or at time of treatment failure, if earlier. If patient is surgically retreated and therefore has UDS prior to 12-months as part of treatment failure battery, UDS are not done again at 12-months.

‡ Post-operative self-report: daily until pain resolves or 4 weeks post-op.

§ Pain exam is done in follow-up only if patient self reports pain; exam is limited to specific areas patient identifies on the questionnaire.

Appendix B. Patient Postoperative Instructions

1. **Light physical activities** including stretching, inside and outside walking, driving, climbing stairs, cooking, dusting, clerical work and visiting friends, as well as, exercise that does not put pressure on the pelvic area are acceptable and encouraged as soon as you feel comfortable with the activity and are not requiring narcotic pain medication.

2. **Refrain from activities which cause you to feel pressure in the pelvic or vaginal area for six weeks after the surgery.** Such activities would include lifting heavy objects (10 pounds or more) from the floor, stepping on platforms more than one foot high, performing exercises such as squats, lunges, leg presses, and impact producing aerobic exercises such as vigorous running and jumping. Light jogging and aerobic machines are acceptable if not accompanied by a feeling of vaginal or pelvic pressure.

3. **Avoid constipation** by eating high fiber foods and drinking adequate fluids. If you are prone to constipation you should consult your physician or his or her staff for an appropriate plan or receive a laxative for as needed use.

4. **You should not resume taking any medications** *for urinary symptoms which were prescribed prior to your surgery.*

5. **Nothing in the vagina until after your examination which is performed six weeks after surgery. For example, no intercourse, tampons, douching, etc.**

6. **Notify your physician** or his or her staff if you have:
   - increasing pain at any site
   - nausea and vomiting
   - fever greater than 100.4°
   - chest pain or shortness of breath
   - dizziness or feeling lightheaded
   - loss of consciousness or inability to walk
   - increased wound tenderness accompanied by redness, swelling, or discharge
   - heavy bleeding with clots
   - *foul smelling discharge*
   - new onset burning with urination, cloudy or bloody urine
   - feeling of inability to adequately empty your bladder

   If you have severe pain in the abdomen or at surgical sites, vomiting, loss of consciousness, chest pain, shortness of breath, severe headaches, *or other symptoms* which *are* of concern to you - **Present to the emergency room** immediately, if you are unable to reach your physician.

7. *Please fill out your **pain assessment** questionnaire at the same time **each day** as you have been instructed to do.*

Appendix C.

Severity[1] Grading

Grade	Definition
I	Any deviation from the normal intraoperative or postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
IIa	Oral administration of drugs other than such allowed for grade I, including antibiotics for wound or bladder infections
IIb	IV administration of drugs other than such allowed for grade I, including antibiotics; blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic or radiological intervention
IIIo	Additional surgical measures required during TOMUS procedure
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

[1] Modified from*:* Dindo D, Demartines N, Clavien PA. Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery* 2004; 240:205-213.

System Categories

System Categories	Examples
ALLERGIES	Drug reaction
CONSTITUTIONAL	Fevers/chills, fatigue, dizziness, headache
DERMATOLOGIC	(Not related to wound), rash, ecchymosis, tape reaction, candida
GI	Ileus, enterovesical fistula, gastritis, constipation, nausea after 24 hours post-op
GU	Vesicovaginal fistula, urethrovaginal fistula, cystitis, pyelonephritis, bladder injury, dysuria, stones, suprapubic pain
MUSCULOSKELETAL	Aches/pains, back pain
NEUROLOGIC	Weakness, paralysis, numbness, CVA, sciatica
PSYCHIATRIC	Depression, suicidal thoughts, hallucinations, delirium
PULMONARY	Pneumonia, atelectasis, (not PE)
CARDIOVASCULAR	MI, a-fib, CHF, arrhythmia
VASCULAR/HEMATOLOGIC	Blood vessel injury, thromboembolic event (DVT & PE), bleeding, DIC
PELVIC	Pain, dyspareunia
WOUND	Infection, mesh erosion, discharge, chronic sinus, hernia
ANESTHETIC COMPLICATION	Spinal headache, laryngospasm, hoarseness, failed intubation