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Design of the Value of Urodynamic Evaluation (ValUE) Trial: A Non-Inferiority Randomized Trial of Preoperative Urodynamic Investigations

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Abstract

Background and Purpose—Urodynamic studies (UDS) are routinely obtained prior to surgery for stress urinary incontinence (SUI) despite a lack of evidence that UDS information has an actual impact on outcome. The primary aim of this non-inferiority randomized clinical trial is to determine whether women with symptomatic, uncomplicated SUI who undergo only a basic office evaluation (BOE) prior to SUI surgery (No UDS arm) have non-inferior treatment outcomes compared to women who have BOE and UDS (UDS arm). Secondary aims are: 1) to determine how often physicians use preoperative UDS results to alter clinical and surgical decision-making, 2)to compare the amount of improvement in incontinence outcomes, and 3) to determine the incremental cost and utility of performing UDS compared with not performing UDS

Methods—After an initial basic office evaluation, women planning surgery for uncomplicated SUI who consent to study participation will be randomized to receive preoperative UDS or No UDS. Treatment will be planned and performed by the surgeon utilizing all the data available to

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For a list of UITN investigators see appendix A

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them. We will compare results from the basic office evaluation (No UDS) with results from the basic office evaluation and preoperative UDS.

Results—The primary outcome will be measured at 12 months using responses to the Urogenital Distress Inventory and the Patient Global Index – Improvement.

Conclusions—Randomized trials comparing the effects of different diagnostic alternatives on treatment outcomes pose study design challenges. A non-inferiority design is appropriate when comparing a less invasive and less expensive alternative with a standard of care approach.

Keywords

Randomized trial; Stress Urinary Incontinence; Urodynamic studies; Non-inferiority trial

INTRODUCTION

Urinary incontinence is a common and costly condition that affects 15% to 50% of women of all ages and significantly impairs quality of life. [1,2] [3] Stress urinary incontinence (SUI) is one of the two major subtypes of urinary incontinence and affects nearly half of these incontinent women. Surgery is one of the most common treatments for SUI; 135,000 inpatient surgeries for SUI were performed in the U.S. in 1998.[4] Urodynamic studies (UDS) are diagnostic investigations often performed preoperatively to better characterize these patient's incontinence symptoms.

Diagnostic testing is intended to guide clinical management and improve outcomes. Despite its widespread use, there is no evidence that preoperative urodynamic testing improves treatment outcomes in women with uncomplicated stress urinary incontinence. Agur et al [5] have suggested that some urodynamic parameters correlate with adverse outcomes such as decreased efficacy, irritative bladder symptoms, or postoperative voiding difficulty. However, results from a secondary analysis of the Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) reported that in 655 women who received urodynamics before surgery, typical urodynamic parameters often given as reasons for performing UDS [e.g. Valsalva Leak Point Pressures (VLPP), presence or absence of detrusor overactivity (DO), urodynamic stress incontinence (USI)] did not predict stress incontinence success or failure, although there was a trend toward a lower success rate in women without USI. [6] In the same group of patients, preoperative UDS measures were unable to predict the likelihood of voiding dysfunction after surgery.[7]

Several professional organizations including the International Urogynecological Association (IUGA) Guidelines for Research and Practice, and the Royal College of Obstetrics and Gynecology (RCOG) recommend performance of UDS prior to surgical management of SUI. Not all professional societies and organizations are in agreement regarding the role of UDS in the preoperative assessment of SUI. In 2006, the National Institute for Health and Clinical Excellence (NICE) in the U.K. states that "the use of multichannel cystometry is not routinely recommended before surgery in women with a clearly defined clinical diagnosis of pure SUI". [8] A large U.K. tertiary referral center has challenged this report noting that only 5% of their patients with urinary incontinence had pure SUI, and of these, a quarter will have other urodynamic diagnoses. These authors suggested that the NICE recommendations are "unwise" and argue that "a randomized trial of preoperative urodynamics is required to inform clinical practice…" [5]. This sentiment for a RCT is supported by an evidence based Cochrane review which concluded that "A larger definitive trial is needed, in which people are randomly allocated to management according to urodynamic findings or to standard management based on history and clinical examination.".[9] In addition to a lack of evidence that preoperative UDS improves outcomes in uncomplicated patients with SUI,

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urodynamic testing has other negatives. It is expensive (approximately $1000 USD), time-consuming (approximately 1 hour), invasive (requiring a urinary catheter), and may be uncomfortable and/or embarrassing to patients.

Although studies are needed to determine the benefits of urodynamic information for all urinary incontinence disorders, there is less controversy about performing UDS preoperatively in women with more complex clinical presentations, including concomitant stress and urge incontinence (symptoms of leakage with a strong urge and leakage with stress provocation, both bothersome to the patient), or those who have failed a previous surgery, as findings may help guide primary approaches to treatment. There is also less controversy about the use of UDS prior to any conservative non-surgical therapy, as it is generally agreed that it is not necessary as the risk-benefit ratio of the proposed therapy has a good therapeutic index. A UDS performed for multiple clinical diagnoses does not answer the question of the value of UDS for a specific diagnosis. Therefore we have designed and implemented a narrower and more feasible study that addresses the role of preoperative UDS for uncomplicated SUI in selected patients desiring surgical intervention for predominant SUI following a basic office evaluation (BOE). We propose to study the clinical utility of UDS in women with stress predominant incontinence because of the high volume use and unresolved benefit of UDS for this condition.

METHODS

Study Design

UDS is currently considered standard of care. This trial is designed to compare a less invasive alternative, a basic office evaluation (BOE) without UDS (No UDS), with standard of care (i.e. a BOE and UDS, or the UDS arm) to determine whether the No UDS arm is non-inferior to the UDS arm. Because we anticipate that any difference seen between the UDS and No UDS groups may be subtle, we selected a randomized, non-inferiority design. By randomly assigning participants to receive UDS or not, confounding factors due to surgeon and patient preferences as well as differences by clinical center will be minimized.

At the conclusion of the study, if the No UDS arm is no more than marginally inferior to the UDS arm, it will be possible to deem the No UDS arm non-inferior to the UDS arm and conclude that UDS is not necessary rather than continuing with it as standard of care prior to surgery in this patient population. If this study was designed as a typical superiority trial and the success rates in the No UDS and UDS arms were very similar, the conclusion drawn would be an inability to detect a difference between the two arms. Such a conclusion would not be the same as finding that the No UDS arm is non-inferior to the UDS arm and, therefore, is less clinically relevant. The design of the trial is depicted in Figure 1.

Randomization

Participants are randomized either to UDS or No UDS using an automated randomization system, with a back-up system of sealed randomization envelopes in the case of technical problems. Randomization is stratified by surgeon with institutional balancing, using permuted blocks. Neither patients nor surgeons are blinded to group assignment.

The protocol was approved by the Data and Safety Monitoring Board (DSMB) of the Urinary Incontinence Treatment Network (UITN) and Institutional Review Boards of all participating centers. Written informed consent is obtained from all women prior to study enrollment. Recruitment is estimated to take approximately 2.5 years following initiation of enrollment which began in November 2008.

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Study Aims

The primary aim of the study is to determine if women who are surgical candidates for treatment of uncomplicated predominant SUI after a basic office evaluation only (No UDS arm) have non-inferior treatment outcomes compared to women who receive both a basic office evaluation and preoperative UDS (UDS arm).

The trial has three main secondary aims. The first is to determine, among women randomized to UDS, how often physicians use UDS to alter clinical decision-making in selecting and/or performing SUI surgery. The second aim is to compare improvement in incontinence outcomes between groups. The third aim is to determine the incremental cost and utility of performing UDS as compared to not performing UDS.

Study Population

The study population consists of women with predominant stress urinary incontinence (SUI) and no history of incontinence surgery. The women are appropriate surgical candidates and are seeking such correction. Inclusion and exclusion criteria are displayed in Table 1.

Physician Diagnosis and Management

Prior to randomization, the surgeon will specify the diagnosis and planned treatment based on results of the basic office evaluation and clinical judgement. If randomized to UDS, the surgeon will report any changes in diagnosis, treatment plan (for example, the plan could change to a non-surgical therapy), or modifications to the existing treatment plan as a result of the additional information provided by UDS.

Measures

Primary and secondary outcomes will be assessed with validated instruments throughout the study. The schedule of measurements is included in Table 2.

Primary Outcome Measure—The primary outcome is measured at 12 months and includes a traditional, objective measure and a patient-oriented subjective report. The Urogenital Distress Inventory (UDI) is a 20-item patient-reported measure, that assesses symptoms of stress incontinence, urge incontinence, urgency, frequency, and voiding dysfunction [10]. This instrument has established validity, reliability, and responsiveness to change. In addition, we selected the Patient Global Index – Improvement (PGI-I) which is a patient-reported measure of perceived improvement after treatment of stress and urge incontinence that has been shown to have good construct validity in incontinence trials.[11], [12] The PGI-I correlates significantly with incontinence episode frequency (r=0.36), pad test weights (r=0.20) and quality of life (IQOL: r=−0.50) in women with predominant SUI. [13] Significant reductions in values are typically observed after SUI surgery. The PGI-I asks subjects to check the one number that best describes how their urinary tract condition (bladder) is now, compared to how it was before they received treatment for urinary leakage. Response choices are: 1) “very much better”, 2) “much better”, 3) “a little better”, 4) “no change”, 5) “a little worse”, 6) “much worse”, and 7) “very much worse”. Specifically, treatment success is defined as a 70% reduction in the UDI from baseline to 12 months and a score of “1” or “2” (i.e., “very much better” or “much better”) on the PGI-I at 12 months. Thus, treatment failure is defined by the occurrence of one of the following: a less than 70% reduction in the UDI from baseline to 12 months or a score of 3 or greater on the PGI-I at 12 months.

Secondary Outcome Measures—Self-reported stress-type urinary incontinence symptoms will be measured using selected items from the Medical, Epidemiologic and

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Social Aspects of Aging Project (MESA).[14] Quality of life measures include general health-related quality of life measured by the Short Form-12 Health Survey and condition-specific quality of life measured by the Incontinence Impact Questionnaire (IIQ-7)[10]. Incontinence severity is measured with the Hunskaar/Sandvik Incontinence Severity Index (ISI) [15] and the Patient Global Impression Index of Severity[13]. Patient satisfaction with treatment outcome is measured with a 5-point Likert scale (very dissatisfied to very satisfied) that asks patients to rate satisfaction with how treatment has affected 1) urine leakage; 2) urine leakage related to feeling of urgency; 3) urine leakage related to physical activity, coughing or sneezing; and 4) frequency of urination. Finally, as it is plausible that patients undergoing UDS will feel more prepared for surgery and the post-operative period than those who do not receive UDS, preparedness is measured with an 11-item questionnaire developed for this purpose.

To measure how often physicians alter their clinical decision making based on the results of UDS, specifically designed data collection forms have been developed to record the surgeons clinical diagnosis, treatment plan, confidence in treatment plan, and patient counseling. These forms are administered after the basic office evaluation and again after UDS for the subjects who were randomized to UDS. Urodynamic results and interpretation, using ICS definitions, are recorded on a separate data form and a final form characterizes any treatment changes or modifications because of UDS findings.

Voiding function is evaluated preoperatively by a post-void residual (PVR). Any use of a catheter and/or medical therapy to facilitate bladder emptying at or beyond 6 weeks post-surgery, or any surgical therapy to facilitate bladder emptying at anytime post-surgery is considered voiding dysfunction. For an objective measure of stress incontinence outcome, a provocative stress test standardized to volume (i.e. 300ml) is performed at the 12 month visit for direct observation of urine leakage.[16] To minimize potential bias, a qualified examiner blinded to the randomization group and not the study surgeon will perform this stress test. Additional treatment and evaluation information will be reported by the patient on specific survey instruments at 3 and 12 months..

Data on medical and non-medical costs are being collected. Direct costs of medical care both within the study (i.e. costs associated with surgery) and medical care utilization outside of the study will be assessed. For study-related care, data are collected regarding type of surgery, number of inpatient days, complications/morbidity (any adverse deviation from the normal intraoperative or postoperative course), medications, and additional therapies. Intervention costs will be calculated as the product of resource utilization and unit costs. Medication cost will be estimated using the minimum average wholesale price of commonly prescribed medications. Marginal use of resources (provider visits) will be estimated between groups. Direct costs will be calculated using a proxy for societal cost, Medicare resource-based relative value scale charges for physician services.

For assessing direct non-medical costs, participants report numbers of pads, protection, laundry, dry cleaning, personal hygiene products, household protection, and household cleaning products consumed specifically for their incontinence. Data are also collected regarding indirect resources related to incontinence (time spent on incontinence-related healthcare, limits on employment or volunteer work due to incontinence). The Incontinence Resource Use Questionnaire was derived from other published expense surveys.[17–19] The average national cost of each product will be determined by a survey of several retail and wholesale stores. Finally, health-related quality of life (utilities) for health outcomes is measured with the Health Utilities Index Mark 3 (HUI3).[20]

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Adverse events are reported in accordance with the Department of Health and Human Services (DHHS) code of federal regulations (Title 45, Part 46). The UITN DSMB meets a minimum of two times per year to monitor all of the Network's trials.

Study Arms

All patients receive a basic office evaluation which is a routine part of the surgeons' preoperative clinical assessment. Core components are standardized per protocol and include the following: self-reported stress-type UI symptoms, a provocative stress test at any volume, post void residual (PVR) by any method, dipstick urinalysis, a standing, straining prolapse exam and assessment of urethral mobility (i.e. by either a Q-tip test, visual inspection, palpation, point Aa on POP-Q exam, or a lateral cystogram).

NO UDS—The patients who after the basic office evaluation randomize to the NO UDS arm will proceed with their planned surgical intervention.

UDS—Patients in the UDS arm receive core urodynamic investigations including non-instrumented uroflowmetry (NIF) with a comfortably full bladder, PVR obtained with catheter (after NIF), filling CMG with VLPP determination attempts, and a pressure flow study (PFS). Testing is performed according to the local high quality standards of urodynamic practices at each study center. Specific testing and procedural details of the core urodynamic procedures conform to ICS Good Urodynamic Practice guidelines[21], and testing results and interpretation of results conform to ICS nomenclature.[22]. Optional UDS investigations (e.g. Urethral Pressure Profiles, Videourodynamics) may be performed if those investigations are customary practice for the patient population at a study center. The UITN has significant experience demonstrating the development of standardized, multi-center, high quality urodynamic studies in previous trials. [23,24]

Sample Size Determination for Primary Endpoint

As a non-inferiority trial, we determined our sample size by defining P_1 as the proportion of women in the UDS arm who have a treatment success (defined by the primary outcome measure) and P_2 as the proportion of women in the No UDS group who succeed. The equivalence margin or delta (δ) is the largest clinically relevant difference that would be allowed for the two arms to differ by and still say that the No UDS arm is non-inferior to the UDS arm. Alpha (α) is the probability of declaring that the No UDS group is not inferior to the UDS group given that the No UDS group is indeed inferior by at least an amount δ. Power is the probability of declaring that the No UDS group is not inferior to the UDS group given that the No UDS group is not inferior. The sample size calculation is performed under the assumption that the treatment success rates for the two groups are identical. It is also assumed that a test of the difference in proportions ($P_1 - P_2$) using the normal approximation to the binomial distribution will be used to determine non-inferiority.

For sample size calculation, we assume an alpha (α) value of 0.05 and that the true proportion of successes in each group is 70% with an equivalence margin or δ of 11%. This equivalence margin was chosen based on the belief that this was the largest amount that we would allow the success rate to differ and still deem the no UDS group non-inferior, while still producing a realistic sample size. Using these assumptions, 270 women are needed in each study arm to have 80% power for determining whether the No UDS arm is non-inferior to the UDS arm (Hintze, J. (2004). NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, UT). To account for a dropout rate of 10%, a sample size of 300 women per arm (600 women total) will be required.

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Analytic Approach for the Primary Endpoint

At the end of the study, we will construct a two-sided 95% confidence interval for the difference in the proportion of successes in the UDS group and the No UDS group ($P_1 - P_2$) to determine whether the No UDS arm is non-inferior to the UDS arm. Decisions regarding non-inferiority will be made according to Figure 2 based on the confidence interval. Should the upper limit of the two-sided confidence interval for the difference be less than the delta limit, only then can non-inferiority for the No UDS group compared with the UDS group be declared. According to Figure 2, this occurs only when the upper end of the confidence limit does not cross the dotted line (the δ value of 11%), as in scenarios 3, 4 and 6. In the two inconclusive scenarios in Figure 2 (scenarios 2 and 5), the confidence limit crosses the δ value, so it is not certain that the No UDS arm is truly non-inferior to the UDS arm. In scenario 1, both the lower and upper limit of the confidence interval exceed δ; in this case, the No UDS group can be declared inferior to the UDS group.

The study plans to also test for the possibility that the No UDS group is not just non-inferior, but superior to the UDS group, while maintaining the planned overall α level of 0.05 [25]. As described above, the test for non-inferiority will be done and non-inferiority will be determined according to the two-sided level 1-α confidence interval. If it cannot be concluded that the No UDS arm is non-inferior to the UDS arm, no further testing will be done. However, if non-inferiority can be concluded as in scenarios 3, 4 and 6, then the same confidence interval will be used to assess whether the No UDS arm is better than the UDS arm. Specifically, if the interval does not overlap zero, then the No UDS arm is deemed superior to the UDS arm (scenario 3). If the interval does overlap zero, then the No UDS arm is still declared non-inferior to the UDS arm.

To minimize bias towards non-inferiority, only women treated “per protocol” will be considered in the analysis of the primary endpoint.[26] “Per protocol” is defined as considering only women in the UDS arm who have UDS performed and only women in the No UDS arm who only have an office assessment (and no UDS); e.g. include only those who receive the assessment that they are randomized to in the analysis. Intention-to-treat (ITT) analysis, which includes all patients by randomization group regardless of the treatment received, will also be performed, but will be considered secondary.

Analytic Approach for the Secondary Endpoints

Descriptive statistics will be calculated to measure how often physicians alter their clinical decision-making based on the results of UDS before a planned intervention. Specifically, the rates of altered diagnoses and number of modifications to the initial treatment will be compared using chi-square tests or t tests, as appropriate. To compare the amount of improvement in incontinence outcomes in women randomized to the two diagnostic methods, the women in the two groups will be compared regarding the two components of the primary outcome: the percent improvement in UDI and PGI-I score. The mean percent improvement in UDI in the two groups and the 95% confidence interval of the difference in the mean improvement between the groups will also be computed. For PGI-I score, ordinal logistic regression analysis will be used to estimate the relative odds of a lower score (more improvement) in the PGI-I of the No UDS vs. UDS diagnostic groups and its 95% confidence interval.

An underlying, but untested, premise of this trial is that availability of UDS results can influence how a physician performs the incontinence surgery and therefore the outcome of surgery. To address this important clinical question, a sub-group analysis will be used to compare the outcomes of women who received surgical treatment in the two randomization groups. For this analysis, a two-sided 95% confidence interval for the difference in the

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proportion of treatment successes between the two arms will be conducted only among women who received surgery. The definition of treatment success for this comparison is the primary outcome measure plus a negative standard volume stress test.

Additional analyses will be performed comparing the two arms in terms of quality of life, urinary incontinence severity, voiding dysfunction, and other measures as necessary. Multivariable linear regression will be used for continuous measures and logistic regression for dichotomous measures controlling for relevant baseline characteristics. P values less than 0.05 will be considered to be statistically significant and no adjustments will be made for multiple comparisons. However, when secondary measures are reported, readers will be informed of the susceptibility to chance findings.

Cost Analysis

Intervention costs will be calculated as the product of resource utilization and unit costs. Standard costs (DRG, CPT, and AWP) will be applied to each utilization. Medication cost will be estimated using the minimum average wholesale price of commonly prescribed medications.[27] Marginal use of resources (provider visits) will be estimated between groups. Direct costs will be calculated using a proxy for societal cost, Medicare resource-based relative value scale charges for physician services.[28] Cost-utility and cost-effectiveness analyses will be performed to compare the two groups. For cost-utility analyses, net cost and net QALY will be estimated in each arm of the model, and the marginal cost per quality adjusted life year (QALY) will be calculated and compared across groups. For cost-effectiveness analyses, we will determine the marginal cost between the groups per treatment outcome.

DISCUSSION

Recent systematic reviews by the National Institute for Health and Clinical Excellence[8] and the Cochrane group[9] have called into question the utility of preoperative UDS for the uncomplicated stress incontinent patient. However, experts do emphasize that this tentative conclusion is derived from flawed and limited evidence in the literature. Consensus expert opinion has called for the development and implementation of a randomized trial to evaluate the utility of preoperative UDS for this surgical population.[5,9] This trial attempts to evaluate the clinical utility of UDS and we found that designing a trial of a diagnostic test poses several challenges.

It is generally accepted in medicine that diagnostic studies are performed for specific indications to answer specific questions. The ultimate value of a diagnostic test is its ability to change clinical decision-making, and by doing so, improve outcomes. An underlying assumption of this current trial is that UDS is a diagnostic tool that may alter clinical diagnosis, change clinical decision-making, and change outcomes in women planning surgery for SUI. If UDS changes the diagnosis, a different treatment is possibly in the best interests of the patient. If UDS reveals that the patient may be higher risk for treatment failure or treatment complication, patient counseling may be different and the treatment may be altered in a way to reduce the risk of a complication. In the design of a study evaluating a diagnostic test the treating physician has to be able to use that test to change decisions and change treatment and these treatments may have different efficacies. Ultimately however, since we are stratifying the randomization by each surgeon, the efficacy will be a product of the decision-making and treatment produced by adding the UDS.

It is possible that UDS improves outcomes by altering diagnosis and treatments so that the efficacy of the SUI treatment is reduced, but the subject has fewer untoward results like urgency, frequency, urge incontinence, or voiding dysfunction. For this reason, our primary

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outcome measure needs to be an instrument that broadly measures bladder storage and emptying function and patient assessment of her urinary condition. For all these reasons, we chose the Urogenital Distress Inventory and the Patient Global Impression Index as measures that can capture these outcomes.

In many ways the design of this study investigating a diagnostic test is similar to study designs of pragmatic clinical trials. Practitioners are given freedom to treat the patients normally, the outcome has to be relevant to everyday life, and we are evaluating the overall "package" of care. [29] We hope that this trial, like a pragmatic clinical trial, will deliver evidence of effectiveness or ineffectiveness in an everyday clinical context. Unlike a standard superiority trial, to minimize bias toward non-inferiority, our primary outcome will be "per protocol" rather than an intention-to-treat analysis, although we will perform an intention-to-treat analysis as a secondary analysis. Also unlike a pragmatic clinical trial, this study could not have broad inclusion criteria. We restricted this study to uncomplicated stress predominant incontinence patients who did not have previous incontinent surgery or prolapse. The reason for this decision is that if complicated patients were included, a result showing inferiority of the No UDS arm does not answer the question if uncomplicated patients would also have inferior outcomes without UDS. In contrast, if this study shows that the No UDS arm has inferior outcomes to the UDS arm then nearly all clinicians would extrapolate those same results to an even more complicated patient population and a strong argument could be made for universal preoperative UDS.

We chose a non-inferiority design for several reasons. We consider UDS before surgery to be the generally accepted standard procedure throughout much of the world. The question to be addressed in this study is whether women diagnosed with uncomplicated stress urinary incontinence following a basic office evaluation and managed without preoperative UDS have non-inferior outcomes compared to those who receive the more invasive and expensive preoperative UDS. When comparing two approaches to diagnostic testing and a less invasive, less expensive diagnostic regimen is being compared to a more invasive, more expensive standard then a non-inferiority design is more appropriate than the typical superiority trial design that is used when studying two different randomized treatments. At the conclusion of the study, it will be determined whether it can be ruled out "beyond a reasonable doubt" that baseline office assessment alone (No UDS arm) is inferior to the baseline office visit plus UDS (UDS arm) by a clinically significant amount. Four possible conclusions will be drawn: 1) No UDS is better than UDS (superiority), 2) No UDS is non-inferior to UDS (non-inferiority), 3) No UDS is inferior to UDS (inferiority), or 4) unable to show that No UDS is either better than or non-inferior to UDS (inconclusive).

For a non-inferiority trial, the primary outcome of the trial is not expected to differ. In this case, with the effectiveness outcome of the cost-effectiveness analysis expected to be the same, the cost-effectiveness analysis can reduced to a cost-minimization analysis where the study of interest is the total cost difference between women who receive pre surgical UDS and those who do not. The less costly assessment will be a preferred choice from the cost standpoint. The study focus will be the incremental cost. That is to say, we are interested in the cost components that are different between comparison arms. Those cost components that are likely to be the same between comparison arms will have zero cost increments; therefore, their information will not be critical to collect if the study budget is the concern.

In superiority trials, early stopping rules are used to monitor for safety and traditionally would stop a trial if a treatment difference is so large that it is unethical to continue treating the other group of patients with the "inferior" treatment. Interim monitoring of the outcomes for making a decision to end the trial early is not appropriate in this trial for several reasons. In non-inferiority trials, such as this one, the argument of stopping the trial early when there

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is definitive evidence of non-inferiority does not apply. Say, for example, that early data suggests that the No UDS arm is non-inferior to the UDS arm. In this case, it is ethical to continue current practice (use of UDS), and one would want extremely strong evidence to abandon a study in favor of changing standard practice. This trial is comparing two commonly used diagnostic assessment methods, not two treatments. Treatment of patients is a matter of each clinician's clinical judgment. Thus, there would be no need to stop assessing patients by one method or the other due to a difference in treatment outcomes. Also, the more invasive of the two arms is the UDS procedure; however, this is current medical practice and thus any adverse events have been well documented. The "less invasive" arm is simply an office visit and does not pose any significant threat to the patients.

As described above, there will not be a formal statistical stopping rule based on the outcome measure and thus the outcomes will not be analyzed until the end of the trial. However, all subjects in the study will be overseen by three levels of protection: the UITN Data Safety and Monitoring Board, the clinical site Institutional Review Board and the local principal investigator. The DSMB will receive twice yearly information on recruitment and retention, data quality, baseline characteristics and adverse events by randomization arm. Using this information, should the DSMB find the trial unsafe due to excessive adverse events, excessively slow recruitment or other unforeseen safety reasons, then they could recommend stopping the trial.

The major strength of this study is that it is designed to address a common condition, and a common preoperative practice for which there is little evidence. A multi-center, multi-surgeon study with the randomization scheme stratified by surgeon minimizes individual surgeon treatment effects and should provide generalizable results for surgeons and this patient population. The potential weakness in this trial is that if the results show that the NoUDS arm is not inferior, these results are only applicable to this population and more complicated patients may have inferior results. Additional studies on more complicated patients would be needed to answer the same question for this group and certainly there are many more complicated SUI patients that are excluded from this trial. The largest groups of women with SUI who are excluded from this are those with previous surgery and those with anterior or apical prolapse. In a large community population, approximately 30% of women with SUI had co-occurrence of pelvic organ prolapse. [30]

CONCLUSIONS

When evaluating women with stress urinary incontinence, preoperative urodynamic studies can be time-consuming, invasive, and expensive. It is not evident that these investigations commonly alter diagnosis, treatment plans, or treatment outcomes. Randomized trials evaluating diagnostic tests are just as needed as randomized trials evaluating therapeutic interventions. Non-inferiority trial designs are most appropriate for these studies especially when differences between groups are anticipated to be small and subtle. A cost – minimization analysis may substitute for a cost-effectiveness analysis. The information obtained from this trial will be helpful in determining the best preoperative management of women with stress urinary incontinence.

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Appendix A- The Urinary Incontinence Treatment Network (UITN)

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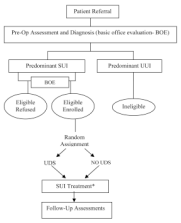

Figure 1.
Trial Design
*Any approved clinical care method Investigators use in their practice.

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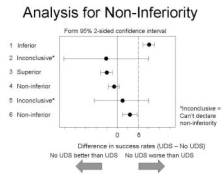

Figure 2.
Examples of Scenarios for Non-Inferiority Trials with Trial Conclusions

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Table 1

Inclusion and Exclusion Criteria in the ValUE study

Inclusion Criteria

1. Female
2. Predominant SUI as evidenced by all of the following:
   - **a.** Self-reported stress-type UI symptoms, of duration ≥3 months
   - **b.** MESA stress symptom score (percent of total possible stress score) greater than MESA urge symptom score (percent of total possible urge score)
3. Observation of leakage by provocative stress test at any volume
4. Eligible for randomization to either treatment group
5. Eligible for SUI surgery
6. Desires non-conservative therapy for SUI
7. PVR <150ml by any method. (May repeat once if initial measure is abnormal)
8. Negative urine dipstick (negative result = trace or less for leukocytes & nitrites) or negative UA or negative culture
9. Available to initiate SUI treatment within 6 weeks of randomization
10. Available for 12-months of follow-up and able to complete study assessments, per clinician judgment.
11. Signed consent form.

Exclusion Criteria

1. Age <21 years
2. Currently undergoing or has had recommended treatment of apical or anterior prolapse
3. No anterior or apical prolapse ≥ +1 on standing straining prolapse exam
4. Pregnant or has not completed child bearing.
5. <12 months post-partum
6. Active malignancy of cervix, uterus, fallopian tube(s) or ovary > Stage I, or bladder of any Stage
7. History of pelvic radiation therapy
8. Previous incontinence surgery
9. Current catheter use
10. Neurological disease known to affect bladder storage (e.g. MS, Parkinsonism, CVA)
11. Previous (i.e. repaired) or current urethral diverticulum
12. Prior augmentation cystoplasty or artificial sphincter
13. Implanted nerve stimulators for urinary symptoms or previous botox bladder injections.
14. Any pelvic surgery within the last 3 months
15. Previous placement of synthetic mesh on a vaginal approach in the anterior compartment
16. Participation in another treatment intervention trial that might influence results of this trial.
17. A urodynamic result reviewed by the investigator in the preceding 12 months or any recollection by the investigator of urodynamic results on that subject.

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Table 2

Schedule of Measurements

	Screen	Baseline	Operative	3 months	12 months
UDI	✓			✓	✓
PGI-I				✓	✓
PGI-S		✓		✓	✓
Stress Test	✓				✓
UDS		✓			
Additional Treatment				✓	✓
SF-12		✓		✓	✓
IIQ-7		✓		✓	✓
ISI		✓		✓	✓
MESA	✓			✓	✓
Voiding Function				✓	✓
Patient Satisfaction				✓	✓
Patient Preparedness		✓			
Adverse Events		✓	✓	✓	✓
Urine Dipstick	✓				
Costs & Utilities		✓			✓
Sociodemographic		✓			
Comorbidities		✓		✓	✓
H&P	✓	✓			✓
PVR	✓				✓
Medication Audit		✓		✓	✓
Prolapse Assessment	✓				
Urethral Mobility	✓				
Operative Measures			✓		
MD Dx & Tx Info.		✓	✓	✓	✓

UDI-Urogenital Distress Inventory[10]; PGI-I- Patient Global Impression of Improvement[11–13]; PGI-S-Patient Global Impression of Severity [11–13]; UDS-Urodynamics; SF-12-Short Form-12; IIQ-7-Incontinence Impact Questionnaire-7; ISI-Incontinence Severity Index[15]; MESA-Medical and social Aspects of Aging questionnaire[14]; H&P- History and Physical; PVR- Post void residual volume; MD Dx- Physician diagnosis; Tx Info- Treatment information.

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