Randomized trial of Retropubic versus Single-incision Mid-Urethral Sling (Altis™) for Concomitant Management of Stress urinary incontinence during Native Tissue Vaginal Repair

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INVESTIGATOR'S SIGNATURE PAGE—Version 20: 1/10/2020

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Investigator: _____
Printed Name and Title

Signed: _____ Date: _____
Name and Title

[PAGE TO BE PRINTED AND SIGNED WITH EACH FINAL PROTOCOL VERSION]

Name and Address of Institution:

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BACKGROUND AND SIGNIFICANCE

Surgical decision making regarding concomitant management of pelvic organ prolapse (POP) and symptomatic or "occult" stress urinary incontinence (SUI) is complex and controversial.[1] One in five women will undergo prolapse surgery in their lifetime, and there is a strong correlation between prolapse and urinary incontinence. [2,3]

Pelvic floor surgeons aspire to improve relevant quality of life outcomes for women with pelvic floor disorders while minimizing complications and unnecessary procedures. Consider the patient who has POP and SUI who undergoes an extensive vaginal repair and synthetic sling and then suffers from prolonged urinary retention post-operatively without a clear answer as to the etiology. Similarly, we have also experienced disappointment and frustration when a patient returns following POP repair with new symptoms of SUI that she ranks as a greater disruption to her quality of life than her original vaginal bulge. Another potential troublesome scenario is a significant surgical complication such as post-operative pain or voiding dysfunction that occurs during the placement of a "prophylactic" sling for "occult" SUI.

Efficacy and risk always compete for equilibrium. Level I evidence has demonstrated a positive efficacy benefit of a concomitant synthetic mid-urethral sling in women with [4], and without [5], pre-operative symptoms of SUI who are undergoing POP repair. Surgical correction of prolapse, with elevation of the vaginal apex and straightening of the angle between the bladder base and the urethra, has the potential to increase existing, or unmask "occult" SUI symptoms.[6]

Concomitant sling placement has been shown to reduce the risk of de novo or persistent SUI from 50% to 23%.[5] The combination of surgical treatment of POP and SUI at the same time, however, increases the risk of incomplete bladder emptying.[5] There is a delicate balance between placing a sling that is tight enough to prevent SUI but loose enough to allow normal voiding function. This is the primary justification of surgeons who employ a staged approach and elect only to treat those who develop bothersome SUI postoperatively.

The type of synthetic sling that is utilized during the combined treatment approach, however, can influence this balance between efficacy and risk. Slings can be placed via the retropubic (RP, see Figure 1), trans-obturator (TO, see Figure 2) or single-incision (SIS, see Figure 3) approaches. While RP slings are considered to be the "gold-standard" referent for other slings with long-term outcomes data [7], they are associated with the highest risks of intra- and post-operative complications including bladder injury, bleeding, and post-operative voiding dysfunction.[8],[9,10] Trans-obturator slings were introduced to avoid the potential complications associated with RP placement. Clinical trials have demonstrated that TO slings are associated with equivalent subjective cure rates to RP slings, with less voiding dysfunction and fewer bladder perforations.[8],[9,11-13] However, TO slings have lower objective cure rates and have greater risk of postoperative

neurologic symptoms in the obturator region.[8,9,12]

Single-incision slings (SIS) are the latest iteration in sling development that build upon the benefits of TO slings but avoid passage through the muscles of the inner thigh. The first prototype SIS was secured behind the symphysis with a metal anchor system and was proven inferior to retropubic slings in treatment efficacy.[4,14] Later designs that employ an anchor system in the obturator membrane demonstrated efficacious one to five-year outcomes with significantly lower risks of voiding dysfunction and thigh pain than TOT slings.[15-18] A reduction in post-operative pain appears highly important to women. Schellart et al evaluated patient preferences for SUI efficacy versus pain and determined that women are willing to trade 4% less efficacy for a significant reduction of 2 days less pain and a 7% reduction in efficacy for 2 weeks' worth of less pain.[19] There is one published trial of concomitant SIS placement at the time of robotic-assisted sacral colpopexy that reported a 0% voiding dysfunction rate and 87% cure at 1 year.[20]

The Altis ™ SIS sling (Coloplast, Minneapolis, MD) consists of a knitted, monofilament, macroporous polypropylene mesh that measures 7.75 cm long. The mesh is characterized by low elasticity (7.5 %), which allows the maintenance of integrity under tension with no banding or cording under the urethra. The system has a fixed anchor on one side and an adjustable anchor on the opposite side. This design is intended to facilitate surgical ease of tensioning the sling: the prolene tensioning suture can be gradually tightened or loosened to achieve the desired effect on the continence mechanism. Clinical trials regarding this particular sling are very limited. Two prospective, non-comparative trials reported cure rates of 84% at 12 months[21] and 81% at 24 months[22], respectively. There were no cases of post-operative voiding dysfunction or groin pain reported in these two trials. At two years, a 3.5% rate of mesh exposure was noted.[22]

As the combination of POP and sling surgery increases the risk of voiding dysfunction, and rates of incomplete bladder emptying appear significantly lower for SIS than RP slings, we hypothesize that the use of the Altis ™ SIS will be non-inferior to RP slings in efficacy and superior in irritative voiding symptoms/voiding dysfunction at one year after combined surgery. The primary objective of this multicenter, prospective, single-blind randomized controlled trial, therefore, is to test this hypothesis for women with objective stress incontinence (symptomatic or occult) who are undergoing native tissue vaginal repair, including colpocleisis. The chosen composite primary outcome of abnormal lower urinary tract function is designed to assess the balanced effects on efficacy versus voiding dysfunction. Secondary outcomes will assess relative differences in pain and complications.

Figure 1: Retropubic sling

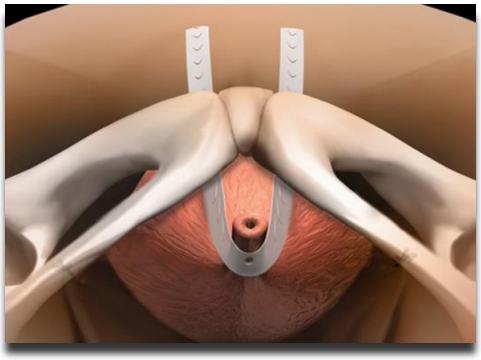

Figure 2: Transobturator sling

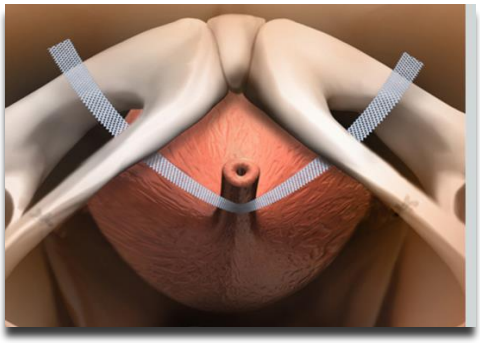

Figure 3: Single-incision sling- blue lines represent where the SIS mesh terminates in the obturator membrane

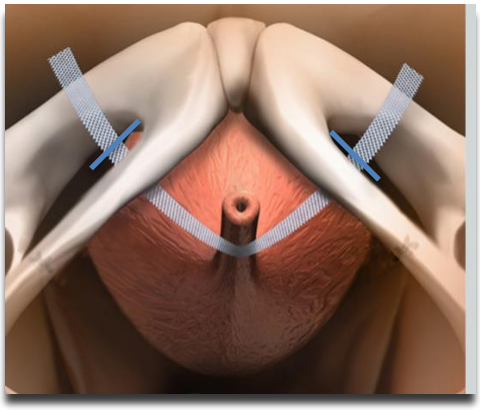

Figure 4: Altis single-incision sling and delivery system

PRIMARY STUDY OBJECTIVES

Hypothesis 1: **Single-incision slings (Altis ™) are non-inferior to Retropubic mid-urethral slings when placed concomitantly at the time of native tissue vaginal repair, including colpocleisis.**

Specific Aim 1:

To conduct a multi-center, prospective, randomized, single-blind trial of retropubic (RP) versus single-incision sling (SIS) in women with ≥ Stage II pelvic organ prolapse and objectively confirmed stress urinary incontinence who are undergoing native tissue vaginal repair.

The **primary outcome** will be **abnormal lower urinary tract function**, a composite outcome defined as the presence of any the following at 1 year post-surgery: subjective stress incontinence symptoms or retreatment for persistent / de novo stress urinary incontinence or retreatment for urinary retention. This study is a non-inferiority study design.

Hypothesis 2: SIS is associated with fewer intra-and post-operative complications up to 1 year following surgery due to fewer sling related complications including urinary tract injury; bleeding; de novo or worsening urge incontinence symptoms; urinary tract infection, mesh exposure, need for prolonged catheter drainage and reoperations than RP slings.

Specific Aim 2:

To compare intra- and post-operative sling related complications, de novo or worsening urge incontinence symptoms and need for prolonged bladder drainage up to 1 year post-operatively in women randomized to RP versus SIS sling at the time of native tissue vaginal repair.

SUBJECT SELECTION

Inclusion Criteria

1. At least 21 years of age
2. Women being considered for a native tissue vaginal repair in any vaginal compartment or colpocleisis
3. POP ≥ stage II of any vaginal compartment, according to the pelvic organ prolapse quantification (POP-Q) system [31]
4. Vaginal bulge symptoms as indicated by an affirmative response to question 3 of the PFDI-SF20 with some degree of bother (answer must be somewhat, moderately, or quite a bit): Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?
5. Positive standardized cough stress test on clinical examination, or on urodynamic testing
6. Understanding and acceptance of the need to return for all scheduled follow-up visits and willing to complete study questionnaires
7. Able to give informed consent

Exclusion Criteria

1. Prior surgery for stress urinary incontinence including mid-urethral sling; Burch/MMK; fascial pubovaginal sling (autologous, xenograft or allograft; urethral bulking injection
2. Status post reconstructive pelvic surgery with transvaginal mesh kits or sacrocolpopexy with synthetic mesh for prolapse
3. Any serious disease, or chronic condition, that could interfere with the study compliance
4. Unwilling to have a synthetic sling
5. Inability to give informed consent
6. Pregnancy or planning pregnancy in the first postoperative year
7. Untreated urinary tract infection (may be included after resolution)
8. Poorly-controlled diabetes mellitus (HgbA1c > 9 within 3 months of surgery date)
9. Prior pelvic radiation
10. Incarcerated
11. Neurogenic bladder/ pre-operative self-catheterization
12. Elevated post-void residual (>150 ml) that does not resolve with prolapse reduction testing (pessary, prolapse reduced uroflow or micturition study)
13. Prior augmented (synthetic mesh, autologous graft, xenograft, allograft) prolapse repair
14. Planned concomitant bowel related surgery including sphincteroplasty and perineal rectal prolapse surgery, rectovaginal fistula repair, hemorrhoidectomy.

STUDY POPULATION, RECRUITMENT AND SCREENING

Study population participants will consist of women having native tissue vaginal repair in any vaginal compartment. Participants must have vaginal bulge symptoms defined by positive responses to a validated instrument, the Pelvic Floor Distress Inventory[23] and Stage II or greater POP in any vaginal compartment as determined by the Pelvic Organ Prolapse Quantification (POPQ) system[24], a validated tool designed to assess the degree of vaginal prolapse. Participants must have objective evidence of stress incontinence on physical examination, with or without prolapse reduction, or on urodynamic testing. Women will be grouped according to whether they have SYMPTOMATIC or OCCULT SUI for randomization purposes.

Study subjects will be recruited from patients who present to the urogynecology clinical sites at Wake Forest Baptist Health, the Women's Health Institute at the Cleveland Clinic, Northwestern, MedStar Washington Hospital Center, Women's and Infants' Hospital of Rhode Island, Atrium Health, and Groote Schuur Hospital at the University of Cape Town, and the private practice clinic of Dr. Jeffery. Wake Forest Baptist Health will serve as the central Data Coordinating Center. Institutional review board (IRB) approval will be obtained at each participating site.

Potential subjects will be identified by members of the sections of Urogynecology and Reconstructive Pelvic Surgery and Benign Gynecology at the respective institutions. Eligible patients who agree to participate will be provided written informed consent administered by the collaborators listed on each Institutional IRB document.

PRE-INTERVENTION ASSESSMENTS:

All women presenting to the participating clinical centers with signs and symptoms of prolapse and objective stress incontinence (symptomatic or occult) will be screened for their eligibility. If eligible and consenting, the following baseline data will be collected on paper forms that will then be transcribed into a secure RedCap database:

1. Demographic data including age, race, BMI, insurance status
2. Health-related quality of life (SF-12), and measurement of Charlson Comorbidity Index
3. Smoking status (Yes or No)
4. POP-Q data
5. Presence of vaginal atrophy (Yes or No)
6. Menopausal status,including current exposure to topical vaginal estrogen, parity, and urogynecologic surgeries
7. Current exposure to anticholinergic medication (Yes or No)
8. Objective assessment of stress incontinence: Clinical or urodynamic assessment is permitted.
    a. **Clinical cough stress test**: Participants that have no prior objective SUI will be instructed to present with a full bladder . If empty, the bladder can be retrograde filled with 300 ml. In the lithotomy position, subjects will be asked to **cough and strain (Valsalva) while the urethral meatus is observed and the POP is reduced.** If no leakage is demonstrated, the reduction cough stress test will be repeated in the standing position. **Women will be categorized as having symptomatic vs occult SUI for sub-analysis and block randomization.**
    b. **Urodynamic testing**: Participants may undergo standard urodynamic testing with prolapse reduction. A cough stress test at bladder capacity will be performed. If no leakage is demonstrated at capacity with the catheters in place, the catheters will be removed and the cough stress test repeated. Valsalva leak point pressures will be recorded.
9. Assessment of post-void residual volume (collected via bladder scan or CIC)
10. A series of instruments will be used to measure symptom bother: the Pelvic Floor Distress Inventory short form-20,[23] Pelvic Organ Prolapse/Urinary Incontinence Sexual Functioning Questionnaire Short Form (PISQ-IR)[25] and PFIQ-7.

NOTE: Standard of care assessments (POP-Q, UDS, PVRs) are valid to use for the study if they were performed within 6 months of the subject signing consent. Also, if any standard of care questionnaires (matching the study questionnaires) were administered within 6 months before signing consent, they may also be used

in the place of baseline questionnaires and not repeated. Dates of assessments just need to be clear if they were not performed the same day as baseline. Also, make sure all assessments required for the study have been performed per baseline visit requirements.

RANDOMIZATION AND MASKING:

A computer-generated random allocation using a randomly permutated block design (10 subjects per block) will be stratified by clinical site and presence of symptomatic versus occult SUI. Randomization will be assigned in the operating room to minimize surgeon and participant bias. While it is impossible for surgeons to be masked to the randomization, participants will be masked during the one-year follow-up period. Dictated operative notes will list the type of sling under procedures as "per study protocol" and then describe the type of sling used within the body of the operative note. Precautions will be taken to minimize unmasking the study groups: Since RP slings require two suprapubic stab incisions, identical sham incision will also be performed in the SIS group. Surgical wound dressings will be identical for all participants. Finally, all participants, regardless of randomization, will have postoperative indwelling urethral catheters until voiding trials are performed.

STUDY INTERVENTION:

The primary intervention is concomitant placement of any full-length macroporous, monofilament polypropylene bottom-up Retropubic Sling (manufactured by Boston Scientific; Ethicon; Caldera; or Neomed) VERSUS Altis™ single-incision sling (Coloplast, Minneapolis, MN) during completion of native tissue vaginal repair, including colpocleisis. If an anterior or apical procedure is planned, the sling must be tensioned following completion of these steps. Prolapse procedures will be recorded but not controlled by study protocol. Participating surgeons are all extensively experienced in RP sling passage and are required to have performed at least 5 SIS procedures prior to enrolling participants in this trial. In order to minimize the risk of altering the urethrovesical angle and the likelihood of postoperative stress urinary incontinence, any anterior repair will be conducted using an incision proximal to the bladder neck level and separate from sling incisions. Allowable techniques for prolapse repair include anterior and posterior colporrhaphy (plication of fibromuscular vaginal tissue), vaginal paravaginal repair, sacrospinous ligament suspension (either of uterus or vaginal apex), uterosacral ligament suspension (either of uterus or vaginal apex, through vaginal or laparoscopic approach) levator plication or colpocleisis. Any use of allograft, xenograft, or synthetic graft material for POP repair will not be permitted.

Standardized technique of RP sling placement

Retropubic procedures will all be performed using the vaginal or "bottom-up" approach as described by the manufacturers (Ethicon; Boston Scientific; Caldera; Neomed). Subjects will be placed in Trendelenburg position, the legs lowered to lithotomy position, and the bladder completely drained. A 1.5 cm incision will be made at the mid-urethra through a separate vaginal incision with lateral dissection with Metzembaum scissors. After placement of both trocars, cystoscopy with a 70-degree scope will be performed to assess for bladder and urethral injury. Surgeons will set the tension of the TVT slings so that a spacer can be placed between the sling and the urethra. Sling tensioning will be performed after anterior and apical prolapse is corrected. Dermabond or steri strips will be applied to the suprapubic exit incisions.

Standardized technique of SIS placement

All surgeons will watch a standardized video regarding SIS sling placement prior to study launch. A 1.5 cm incision will be made at the level of the mid-urethra, The sling/needle assembly is advanced behind the ischiopubic rami in a transobturator trajectory toward the obturator space bilaterally.The needle is then removed by simply sliding the fixating tip back out. The other side is then completed in an identical fashion. The sling will be tensioned so that it will lie in direct apposition to the urethra but will still permit passage of an instrument between the mesh and the urethra. The adjustment thread is then cut short and the vaginal incision is closed with an absorbable suture.

Following SIS placement, **2 small superficial skin incisions will be made in the same location as the exit sites of a RP sling.** Dermabond or steri strips will be applied.

Any intra-operative adverse events will be recorded on data collection forms.

Post-operative care and procedures for voiding trials will not be standardized. Day of discharge and method of voiding (spontaneous, self-catheterization, suprapubic catheter, or indwelling foley) will be recorded.

POST-INTERVENTION ASSESSMENTS:

The primary study endpoints will be assessed at 6 weeks and 12 months after the index surgery via a clinic visit and health-related quality of life interview/completion of questionnaires. Individual site study coordinators will collect follow-up healthcare utilization data and update the medical history at 6 and 12 months. Study coordinators will complete a telephone interview at 6 months to assess for any Adverse Events.

Clinical outcomes

This trial has a composite **primary** dichotomous outcome of **abnormal lower urinary tract function** at 12 months post-operatively (YES or NO) that is defined as ANY of the following:

1. Subjectively bothersome stress incontinence symptoms at 12 months post-operatively, as measured by a positive response of > 1 to Question 17 on PFDI-20.

2. Any retreatment for stress incontinence including pelvic floor physical therapy; incontinence pessary; urethral bulking injection; repeat incontinence surgery

3. Surgical intervention for urinary retention (sling lysis or revision) at any time point post-operatively

Secondary outcome measures will assess the degree to which the study intervention influences adverse events intra- and post-operatively and will include the following:

1. Adverse events

2. De novo (new affirmative response of > 1 to Question 16 on PFDI-20) or worsening urge incontinence symptoms (increase of score on Question 16 by 2 points or more on PFDI-20) at 12 months post-operatively.

3. Surgeon satisfaction with the sling will be assessed immediately post-operatively with a 10-point VAS.

4. Patient Global Impression of Improvement (PGI-I) Scale for incontinence symptoms.[26]

5. Need for bladder drainage beyond 6 weeks post-operatively

POWER CALCULATION:

This study is a non-inferiority study design. The null hypothesis is that the difference in the proportion of women with abnormal bladder function in the SIS group compared to RP sling group is 12% or more (noninferiority margin: H0: RP-SIS_ 0.12). Based on criteria used in a previously published multicenter trial of mid-urethral slings, we chose a noninferiority margin of 12%. Assuming a subjective cure rate for RP of 82%,127 individuals in each group will provide 80% to reject the null hypothesis (H0) that the true difference in cure rates between the two procedures (% cure RP and % cure ALTIS SIS sling) is less than or equal to 12% in favor of the alternate hypothesis (H1: SIS-RP_ 0.12) that the true difference

in proportions is greater than 12% using a two-group large-sample normal approximation test of proportions with a one-sided 5% significance level. Assuming a 10% loss to follow-up or drop-out rate for the duration of the study, the total enrollment goal is 280. Non-inferiority was declared if the upper bound of the 95% confidence interval for the between group difference in bladder function was less than 12%. To minimize bias toward non-inferiority, only women treated per protocol (ie: underwent the randomized sling) were considered in the primary outcome analysis. A secondary analysis of the primary outcome was performed on the intent to treat population. Likewise, other secondary outcome measures were performed on the intent to treat population.

CALENDAR OF EVENTS

	Baseline	Surgery	Day of DC	2 weeks	6 weeks	6 months	12 months
Informed Consent	X						
CRF	X	X	X	X	X		X
Demographic information	X						
Charlson Comorbidity Index	X						
POP-Q	X				X		X
PFDI-20 short form	X				X		X
PFIQ -7 short form	X						X
PISQ-IR	X						X
Quality of Life measure (SF-12)	X						X
Randomization		X					
Assessment of voiding function			X	X	X		X
PGI					X		X
VAS of Surgeon ease of use of sling		X					
Adverse events		X	X	X	X	X	X

DATA COLLECTION & MANAGEMENT

Data collection will occur at each site at each visit outlined in the Calendar of Events. All study data will be recorded on data collection forms provided by the coordinating site and securely maintained at each site. Any discrepancies between data collection forms and supporting source documents such as physician's notes should be explained on the forms. Any changes made to original entries on data collection forms should be crossed through with a single line and initial and dated by the person making the correction. Do not obscure the original entry.

Data will be entered by study staff at each site into a REDCap database (described in detail in the "STUDY SUBJECT PROTECTION" section of this protocol) that will be stored on a secure server by the data coordinating center. Study data source documentation and progress notes will be monitored by the data coordinating center as outlined in the "STUDY MONITORING AND DOCUMENTATION" section. Data collected from visits should be entered into REDCap within 5 business days. Any queries to data entered into REDCap should be addressed within 5 business days. Each site should regularly check REDCap for queries.

Each site will maintain all essential study documents in original format and source documentation that support the data collected on study participants in compliance with ICH/GCP guidelines. Documents must be retained until at least 2 years have elapsed since the formal discontinuation of the clinical investigation. Each site will be responsible to ensure that these essential documents are retained and are not accidentally damaged or destroyed prior to the required elapsed time.

STUDY MONITORING AND DOCUMENTATION

Study Monitoring

The Principal Investigator at the data coordinating center will monitor the study and assess the need for amendments as the study progresses. If a protocol revision is necessary for reasons including but not limited to the rights, safety, or welfare of participants, or scientific integrity of the data, an amendment is required. IRB or equivalent approvals of the revised protocol—and if necessary, revised informed consent—must be obtained prior to implementation at each site.

Data Monitoring

Monitoring will be conducted by the data coordinating center throughout the study to ensure that the study is conducted in accordance with the study protocol, Good Clinical Practice, and applicable regulations. By verifying source data, monitoring

helps to safeguard subject safety, ensure data quality, and provide ongoing training and support to ensure compliance.

Semi-annual data verification will be conducted by the data coordinating center to verify that data entry into REDCap is accurate, and to assess compliance with the study protocol requirements. Study data will be source verified for roughly 25% of each site's over all data collection efforts. The data coordinating center reserves the right to monitor more often or a higher percentage if a problem is identified upon verification of the 25%. Site investigators and study personnel must guarantee access to copies of redacted source documents including medical records and auxiliary source documents that support progress note entries. Requests for de-identified/redacted progress notes and supporting documents from each site will be supplied via email at least 10 days prior to the deadline. Other monitoring activities include but are not limited to reviewing informed consent/research authorization forms, adverse event documentation, and protocol deviation reports. Any action items or data queries generated by the data coordinating center after monitoring should be resolved within 5 days.

In the event that a site is notified of a regulatory inspection, sites should immediately contact the data coordinating center (WFBH). The data coordinating center will manage the REDCap database, as well as monitor quality assurance for data entered by each site.

Protocol Deviations

Protocol deviations must be documented on the protocol deviation CRF provided by the coordinating site, logged in each site's protocol deviation log, and entered into REDCap. Protocol deviations will be documented in sequential order **according to site**—not by individual patient—and they will be entered into REDCap.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventative actions (including notification, site re-training, or discontinuation) will be put into place by the principal investigator.

Site staff must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Site staff shall notify the PI and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Local IRB/regulatory requirements will prevail if sooner than 5 working days. All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Data Coordinating Center. Study sites may also be required to report deviations to their IRB per local guidelines and government regulations.

Data Safety Monitoring Board

A data safety monitoring board (DSMB) will be established that is made up of two independent physicians with no connection to the conduct of this clinical trial who have no relevant conflicts of interests. The PI will review the DINDO grading of any sling related post adverse events within 48 hours of reporting and will immediately report these events to the DSMB. The DSMB will receive a progress report of study recruitment, enrollment, and retention every 6 months and make a determination regarding appropriate continuation of the study.

REPORTING ADVERSE EVENTS:

Adverse events will be recorded and reported according to criteria and timeline below. Sites will also follow local regulatory standards for AE reporting.

All study-related AEs must be recorded on the AE CRF supplied by the coordinating site, entered into the site AE log, then entered into REDCap. Each AE will be sequentially numbered according to patient. For example, patient 003's first AE would be 003.01. Each site investigator will determine the relationship of the AE to the operative procedures, the relationship of the AE to the device, along with the severity of each reportable AEs. All complications will be evaluated by the sub-sites with PI (CAM) being the deciding factor for the DINDO score (See Table Below). The sub-sites will also determine if the complications are more likely to be related to the overall surgery, sling surgery or both. Complications that are deemed not related to the surgery will be excluded (For example, a MI at >3mo postop.)

SAEs must be reported to the DSMB within two business days as outlined above in the DSMB section.

TABLE 1. Classification of Surgical Complications Clavien-DINDO Grade Definition for Sling attributed post-op events only

Grade 1	Any deviation from the normal postoperative course without the need for pharmacologic treatment. Allowed therapeutic interventions are: drugs as antiemetics, antipyretics, analgesics, physiotherapy
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention

IIIA IIIB	Intervention not under general anesthesia Intervention under general anesthesia
Grade IV IVA IVB	Life-threatening complication (including CNS complications)* requiring IC/ICU management Single organ dysfunction (including dialysis) Multiorgan dysfunction
Grade V	Death

Protocol Specific Reportable AEs include those determined to be related to the operative procedures or the device as listed below:

Bleeding
Bladder Injury (Cystotomy or Bladder Trocar Perforation)
Vaginal Wall Perforation
Urethral Injury
Bowel Injury
Nerve Injury
Intestinal Injury
Infection (UTI, Vaginal, Pelvic Abscess)
Bowel Obstruction
Venous Thromboembolism
Mesh Exposure
Leg Pain or Difficulty Ambulating
Fistula
Urinary Retention
Hematoma
Bladder Outlet Obstruction
Urgency “de novo”
Stress or Urgency Incontinence (New or Worsening)
Recurrent POP
Other Urogynecologic Complications: _____

Please note that underlying diseases are not reportable as AEs unless there is an increase of severity or frequency during the course of the study. If an AE has not resolved at the time of AE Form completion, save form as incomplete in REDCap until resolved. Once resolved, update AE form, and enter into REDCap and save form as complete.

Adverse Event Definitions:

Adverse Event: any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory finding) in subjects, whether or not related to the operative procedures

Serious Adverse Event: an adverse event that:

- Led to death
- Led to serious deterioration in the health of the subject that either resulted in
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or a body function
    - in-subject or prolonged hospitalization of existing hospitalization
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

Relationship of AE to Operative Procedures:

Unrelated: No evidence that the timing if the AE has a relationship to the operative procedures performed.
Possibly Related: The AE has a timely relationship to the operative procedures performed, however a potential alternative etiology may be responsible for the AE.
Probably Related: The AE has a timely relationship to the operative procedures performed and the causative relationship can clearly be established. No potential alternative etiology is apparent.

Adverse Event Severity:

Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

Relationship of AE to Device:

Unrelated: No evidence that the timing if the AE has a relationship to the device placement.
Possibly Related: The AE has a timely relationship to the device placement, however a potential alternative etiology may be responsible for the AE.

Probably Related: The AE has a timely relationship to the device placement performed and the causative relationship can clearly be established. No potential alternative etiology is apparent.

STUDY SUBJECT PROTECTION

Protection of each subject's personal health information will be a priority in this study. One master Excel file containing subject personal information including name and medical record number will be kept in a password-protected file, on a designated protected research drive on a password-protected computer in a locked office at each respective institution. In that file, each subject will be assigned a subject identification number that will be used for the purposes of data collection in order to de-identify subjects.

All paper forms used for data collection will be kept in a research cabinet dedicated to this project, which will be locked at all times, in a locked office at Wake Forest Baptist Health (or other institution). All forms will contain de-identified information when sent to the monitoring site. Identification numbers will correspond to the subjects listed in the master excel file.

All study data will be transferred and managed electronically using REDCap (Research Electronic Data Capture). Each subject will be entered into REDCap using the assigned identification number from the master excel file. REDCap is a secure, web-based application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation, audit trials, and a de-identified data export mechanism to common statistical packages. The system was developed by a multi-institutional consortium that was initiated at Vanderbilt University and includes Wake Forest Baptist Health. The database is hosted within the Clinical and Translational Research Unit at Wake Forest and is managed by the Quantitative Health Sciences Department. The system is protected by a login and Secure Sockets Layers (SSL) encryption. Data collection is customized for each study as based on a study-specific data dictionary defined by the research team with guidance from the REDCap administrator in Quantitative Health Sciences at Wake Forest.

AUTHORSHIP

For the primary paper, Dr. Matthews will serve as first author, Dr. Gutman as second author for contributions made to study design and protocol development, and Dr. Roovers as senior author for statistical analysis and protocol development. All site PIs will be listed as authors, in addition to the top 3 recruiting Co-Investigators, in order of recruitment volume.

All investigators will have equal access to the primary data set for secondary analyses. A research design will have to be submitted to the study PI to ensure no duplication of effort. For any secondary analyses, Dr. Matthews will serve as

the senior author and only those members of the group involved in the secondary analysis will be listed as authors on any subsequent papers.

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