Permanent Versus Absorbable Colpopexy Trial (PACT)

NCT number: NCT02277925

Document Date: 02-18-16

Permanent versus delayed-absorbable monofilament suture for vaginal graft attachment during minimally-invasive total hysterectomy and sacrocolpopexy: A Randomized Clinical Trial

Principal Investigator: Catherine Matthews, MD

Wake Forest Baptist Health, Winston-Salem, NC

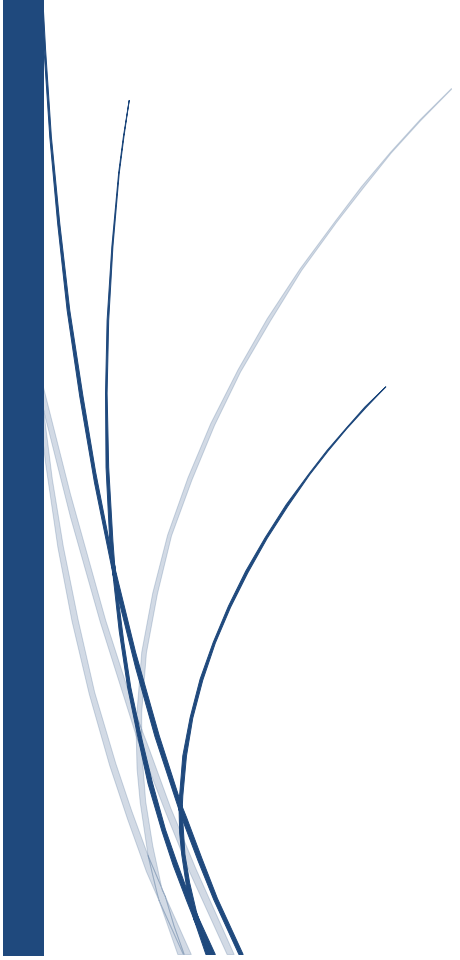
Co-Investigators: Elizabeth Geller, MD

Jennifer Wu, MD, MPH

Kimberly Kenton, MD

Brent Parnell, MD

Erinn Meyers, MD



Contents

STUDY AIMS

Primary Aim:

The primary aim of this randomized controlled trial (RCT) is to compare vaginal mesh and suture exposure rates in women undergoing robotic total hysterectomy and sacrocolpopexy with a light-weight polypropylene mesh (Upsylon™ y-mesh) using either permanent suture (polytetrafluoroethylene, Gore-Tex) versus delayed absorbable monofilament suture (polydioxanone, PDS) through1-year post surgery.

Secondary Aims:

1. To compare the 1-year composite success rate (*leading edge of prolapse is at or above the hymen and apex has descended less than 1/3 of the vaginal length, no subjective feeling of bulge; no retreatment for pelvic organ prolapse* (POP); *no vaginal mesh/suture exposure*) of permanent versus delayed absorbable sutures for mesh graft attachment during robotic total hysterectomy and sacrocolpopexy.
2. To compare postoperative symptoms of pelvic floor disorders, including urinary incontinence, voiding dysfunction, pelvic organ prolapse, sexual dysfunction and quality of life between the 2 groups at 1 year.
3. To evaluate adverse outcomes in each group, classified according to the Clavien-Dindo system.

BACKGROUND

Symptomatic pelvic organ prolapse is common and 13%[1] to 19%[2,3] of women undergo surgical repair. Reconstructive pelvic surgery is broadly divided into procedures that rely on existing native tissue versus the use of graft augmentation, either with synthetic or biologic materials. Native tissue vaginal repair, while associated with the lowest rate of surgical complications,[4] has a high rate of recurrent prolapse. A recent randomized trial of uterosacral versus sacrospinous ligament fixation for POP demonstrated a 30% recurrence rate at 2 years.[3]

Abdominal sacrocolpopexy (SCP) is considered to be the most durable operation for advanced pelvic organ prolapse with reoperation rates of less than 5%.[5-7] Minimally-invasive techniques of SCP, such as robotic-assistance, are associated with improved recovery times and less cost than abdominal SCP without a demonstrable difference in efficacy.[8,9] While traditionally reserved for women with vaginal vault prolapse, SCP is increasingly considered as a primary surgical option for women who present with uterovaginal prolapse in an attempt to improve longer-term surgical outcomes. The optimal management of the uterus and cervix in these cases is unclear.

Rationale for total versus supracervical hysterectomy with concomitant SCP

While supracervical hysterectomy and concomitant SCP are associated with lower rates of mesh exposure,[10-12] potential negative consequences of a supracervical hysterectomy include morcellation of unanticipated uterine malignancy,[13] cervical stump prolapse/elongation, cyclic vaginal bleeding, and reduced anterior vaginal support (Myers EM, Matthews et al., in press). When conducting a supracervical hysterectomy, power morcellators are the most common method used to extract the amputated uterine corpus. The potential risks of power morcellation were recently highlighted by the FDA safety notification which focused on the potential to disseminate fragments of an undiagnosed uterine leiomyosarcoma throughout the abdomen, which negatively impacts prognosis (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm393576.htm). With these

recent developments the focus has shifted towards performing total hysterectomy for delivery of an intact specimen through the vagina.

Vaginal mesh exposure has been a problematic complication with both abdominal SCP and minimally invasive SCP. Widely disparate rates of mesh exposure ranging from 0%[14] to 27%[15] have been reported. A systematic review of ASCP outcomes in 2004 reported an overall rate of 3.4%,[6] and a recent meta-analysis of robotic-assisted SCP reported an overall rate of 2%.[16] Some consistent risk factors for mesh exposure are non-Type 1 polypropylene mesh (knitted, small-pore mesh materials) and smoking.[17,18] Some studies have identified total hysterectomy as a significant risk factor. In an evaluation of patients enrolled in the CARE trial, 6% had evidence of mesh exposure at 2 years, with concomitant hysterectomy presenting almost a 5-fold increased risk.[18] The rate at 6 years rose to 10.5%. [5] More than 50% of subjects in this trial, however, had a non-Type 1 polypropylene mesh. Akyol et al. demonstrated a 2-fold increased risk (12%)[19] and Bensinger et al. a 7-fold increased risk (8.2%)[20] of concomitant total hysterectomy. In contrast, 4 retrospective studies in which Type1 polypropylene mesh was used revealed no increased risk of mesh erosion with concomitant total hysterectomy.[14,21-23] These widely discrepant rates of mesh exposure may be related to surgical technique, graft material and/or suture materials used for mesh attachment.

Rationale for need to study suture material for mesh attachment during SCP

The effect of suture on mesh exposure may be as significant as concomitant hysterectomy or mesh type. At UNC, we reported on mesh exposure using a permanent suture for mesh attachment during SCP with and without concomitant total hysterectomy, with rates of 8% at 1 year.[24] There is some evidence that a delayed absorbable suture may reduce the risk of mesh or suture erosion. In a retrospective review comparing braided permanent suture to delayed absorbable monofilament suture for SCP mesh attachment, rates of mesh exposure were reduced in the absorbable suture group (3.7% vs 0%), with no associated POP recurrence.[25] Similarly, in another retrospective review, when delayed absorbable monofilament suture was used for SCP mesh attachment in 67 women undergoing total abdominal hysterectomy and SCP, no mesh exposures were noted at a median follow up of 27 months.[26] The use of permanent sutures for vaginal mesh attachment has historically been advocated as a means to reduce POP recurrence risk; yet, no prospective study has definitively answered this question. The tradeoff of using a permanent suture may be an increased risk of mesh or suture exposure, as a permanent suture that has breached the vaginal epithelium may serve as a nidus for bacterial seeding, theoretically increasing the risk of mesh exposure. **As SCP appears to be a more durable procedure for women with advanced uterovaginal prolapse, there is an urgent need to identify the ideal method of vaginal mesh attachment that minimizes the risk of mesh-related complications while maintaining effectiveness of the POP repair.**

Choice of mesh material

Upsylon™ (Boston Scientific, Natick, MA) is a pre-formed Y-mesh that is light-weight (25 g/m^2), composed of Type I polypropylene material, with a pore size of 2.8 mm^2 and surface area ration of 1.11. It was FDA approved in 2012. The mesh is blue in color that may aide in the ability to detect even small areas of mesh exposure and erosion. No data currently exist regarding the performance of this particular mesh product in SCP. It is lighter in mesh weight than the IntePro™ y-mesh (American Medical Systems, Minneapolis, MN), which we previously used in the comparative trial of robotic to abdominal SCP in which our mesh exposure rates were 8%.

The primary aim of this randomized trial, therefore, is to test the hypothesis that use of the Upsylon™ mesh with a delayed absorbable suture for mesh attachment at the time of robotic-assisted total laparoscopic hysterectomy and SCP will reduce the risk of vaginal

mesh and/or suture exposure rates compared to a permanent monofilament suture. Secondary aims will include an evaluation of the effect of this light-weight mesh and absorbable suture on prolapse and quality of life outcomes and surgical complications at 1 year after surgery.

STUDY DESIGN AND METHODS

This is a randomized controlled trial that will be conducted at 5 clinical sites:

1. The University of North Carolina, Chapel Hill
2. Northwestern Medical Center, Chicago
3. Augusta University, Augusta
4. Wake Forest Baptist Health, Winston-Salem
5. Carolinas Healthcare System, Charlotte

Human Subject Research & Informed Consent

Signed IRB approved consents will be obtained from each participant at the time of enrollment prior to any study-related assessments. The informed consent form will describe the study in detail, as well as the planned and permitted uses, transfers, and disclosures of the subject's personal health information. The objectives of the study and data collection will be explained to every prospective participant prior to enrollment. The participant will be given ample opportunity to inquire about details of the study to decide whether or not to participate. Copies of the informed consent form will be provided to the participant and original documents filed at each study center as per regulatory requirements.

Participants have the right to:

- Withdraw or refuse participation without prejudice at any time during the study
- Voluntarily participate in the study
- Understand the risks and benefits of the study
- Maintain confidentiality of personal medical information
- Receive new information about the study as it becomes available

Participant Screening & Point of Enrollment

Participants may be approached for recruitment once they have decided to undergo surgical repair of symptomatic uterovaginal prolapse with hysterectomy and SCP and have undergone a standard history and physical examination, including a systematic evaluation of prolapse utilizing the pelvic organ prolapse quantification (POP-Q) system.[27] Participants will be screened against the inclusion and exclusion criteria, and if confirmed to meet all requirements will be eligible to be consented for enrollment into the study.

Participants will be considered enrolled in the study once the initial abdominal incision is made. All enrolled subjects will be considered part of the Intent-to-Treat (ITT) population for the final study analysis. All subjects enrolled who are treated with a study procedure will be considered part of the Per Protocol analysis.

The Screening & Enrollment Log will be completed by each site and emailed to the Project Manager on the first Monday of each month.

Study Withdrawal

Participants may withdraw consent at any point during the study. If a participant withdraws or is withdrawn, documentation will be made on an End of Study Form, including the reasons for withdrawal. There is no risk to participants who choose to withdraw from the study. Withdrawn study participants will be included in the Intent-to-Treat analysis and will not be replaced.

Pre-operative/Baseline Visit

The Pre-operative/Baseline Visit may occur up to 3 months prior to surgery. Once consented, subjects will be assigned a subject identification number that consists of a site letter (A-E) and a three-digit identification number.

At this visit participants will complete standardized and validated symptom bother (PFIQ-sf7), sexual functioning (PISQ-IR), and QoL questionnaire (PFDI-sf20) to assess baseline functioning. Preoperative urodynamic testing, imaging, anorectal manometry and/or cystourethroscopy may be completed at the discretion of the physician. Participants who do not meet the inclusion and exclusion criteria are considered screen failures. Information on screen failures will be captured within a case report form (CRF) and will include reasons for screen failure.

The Baseline Visit consists of the following:

- Informed Consent
- Participant Contact Form
- Inclusion/Exclusion Form
- Medical & Surgical History Form
- POP-Q Exam
- PFIQ-sf7, PISQ-IR, PFDI-sf20 questionnaires
- Assessment of pain and analgesic use

Please note that source data collected as part of routine clinical care may be used to complete CRFs as long as the window between prior data collection and operative procedures does not exceed six months. This includes previously performed POP-Q exams as well as previously collected questionnaires.

Randomization

Randomization will be assigned using RedCAP in the operating room *immediately prior* to mesh graft attachment to the vagina. Both types of sutures will be available at each site. Participants will be randomized to 2-0 GoreTex/CV4 GoreTex (depending on availability of Stitchkit) versus 2-0 PDS in blocks with block sizes of 2, 4 and 6 for each of the 5 sites. Randomization will be stratified by site.

Surgery (≤ 3 months from Baseline Visit)

Study data for the surgical procedures includes the Surgical Procedures Form and review of adverse events.

- Surgical Procedures Form
- Review of Adverse Events (if applicable)

Laparoscopic or Robotic Approach

Prior to sacral colpopexy all participants of the trial will undergo total laparoscopic hysterectomy (with or without robotic assistance) with or without bilateral salpingoophorectomy (at the discretion of the patient and surgeon).

Laparoscopic sacral colpopexy will be performed with or without robotic assistance. The configuration of the incisions is not standardized.

1. Total laparoscopic hysterectomy (with or without robotic assistance) will be performed in standard fashion and the uterus will be delivered through the vagina with no power morcellation performed. The vaginal cuff will be closed using an absorbable suture in 1 layer (suture type at the discretion of the operating surgeon). Closure of the vaginal cuff through a transvaginal approach is not allowed.
2. The same ultra-lightweight Type 1 polypropylene mesh (Upsylon, Boston Scientific) will be used for all study subjects.
3. Graft placement on the vagina includes placement on the anterior and posterior vaginal walls. The vesicovaginal and rectovaginal spaces will be opened. The anterior graft will have an attachment that is at least 4 cm long on the anterior vagina with at least 4 sutures. The graft can extend toward the urethrovesical junction but not beyond the UVJ. The posterior graft will be at least 4 cm long and attach to the posterior vagina with at least 4 sutures placed on the posterior vaginal wall. The posterior graft can extend toward the perineal body but cannot be anchored into the perineal body. The sacral arm of the mesh must be attached directly to the anterior longitudinal ligament with at least **2 permanent sutures** (suture type at the discretion of operating surgeon).
4. Closure of the peritoneum over the mesh may be done at the discretion of the operating surgeon.
5. Diagnostic cystoscopy is required after completion of case to confirm intact urothelium and patent ureters.

Optional Additional Procedures

Midurethral sling for treatment or prevention of stress incontinence

1. The surgeon can use any type of full-length mid-urethral, monofilament, polypropylene, sling (retropubic or transobturator).
2. The sling should be done through a separate incision from any other proximal anterior vaginal wall incisions, and dissection should not extend distal to the urethrovesical junction.

Posterior colporrhaphy

1. Posterior repair may be performed at the discretion of the surgeon if the patient has posterior wall prolapse following the apical support procedure as indicated by Bp ≥ -1 on non-straining exam under anesthesia.
2. The surgeon may use a traditional posterior colporrhaphy or defect directed technique.

Anterior colporrhaphy

1. Anterior colporrhaphy may be performed at the discretion of the surgeon if the patient has anterior wall prolapse following the apical support procedure, Ba ≥ -1 on non-straining exam under anesthesia. Otherwise it is at the discretion of the surgeon.

Urethropexy

1. Robotic/laparoscopic urethropexy may be performed at the discretion of the surgeon.

Follow-Up Visits

Participants will be scheduled for follow-up visits as outlined in Table 1 (Data Collection Schedule) below. The follow-up visit schedule begins from the day the subject is discharged (e.g. leaves hospital/clinic) post-procedure and includes visit windows counted in calendar days.

Participant contact information will be reviewed at each follow-up visit. All efforts will be made by site staff to ensure minimal loss to follow-up of participants and will follow a site-specific loss to follow-up plan. This plan may include efforts such as telephone follow-up, Investigator-patient counseling, visit reminder tools, patient stipends, and/or other communication methods.

Week 6 Visit (-2 weeks/+4 weeks)

The primary outcome assessed at the Week 6 visit is evidence of suture or mesh exposure at the site of the sacrocolpopexy mesh. The POP-Q examination will be performed, as well as a vaginal examination (speculum and digital) to assess for suture or mesh exposure. In addition, pain and analgesic use and adverse events will be reviewed. All efforts will be made by site staff to ensure both follow-up anatomic measurements (POP-Qs) will be conducted by a healthcare provider other than the treating surgeon to reduce bias on outcomes after the study procedure. In the event the treating surgeon is the only qualified healthcare provider at the site trained in the POP-Q, the follow-up anatomic measurements will be conducted by the treating surgeon.

The Week 6 Visit consists of the following:

- Participant Contact Form update
- Assessment of pain and analgesic use
- Review of Adverse Events (if applicable)
- POP-Q Exam
- Vaginal examination (speculum and digital) to assess for suture or mesh exposure

Month 6 Phone Call (±4 weeks)

Patients will be contacted by phone 6 months postoperatively to review contact information, pain and analgesic use, and adverse events.

The Month 6 Call consists of the following:

- Participant Contact Form update
- Assessment of pain and analgesic use
- Review of Adverse Events (if applicable)

Year 1 Visit (±4 weeks)

The primary outcome assessed at the Year 1 visit is evidence of suture or mesh exposure at the site of the sacrocolpopexy mesh. The POP-Q examination will be performed, as well as a vaginal examination (speculum and digital) to assess for suture or mesh exposure. In addition, pain and analgesic use and adverse events will be reviewed. Participants will also complete the PFIQ-sf7, PISQ-IR, and PFDI-sf20. All efforts will be made by site staff to ensure both follow-up anatomic measurements (POP-Qs) will be conducted by a healthcare provider other than the treating surgeon to reduce bias on outcomes after the study procedure.

In the event the treating surgeon is the only qualified healthcare provider at the site trained in the POP-Q, the follow-up anatomic measurements will be conducted by the treating surgeon. The End of Study form will also be completed by site staff.

The Year 1 Visit consists of the following:

- Assessment of pain and analgesic use
- Review of Adverse Events (if applicable)
- PFIQ-sf7, PISQ-IR, PFDI-sf20 questionnaires
- POP-Q Exam
- Vaginal examination (speculum and digital) to assess for suture or mesh exposure
- End of Study Form

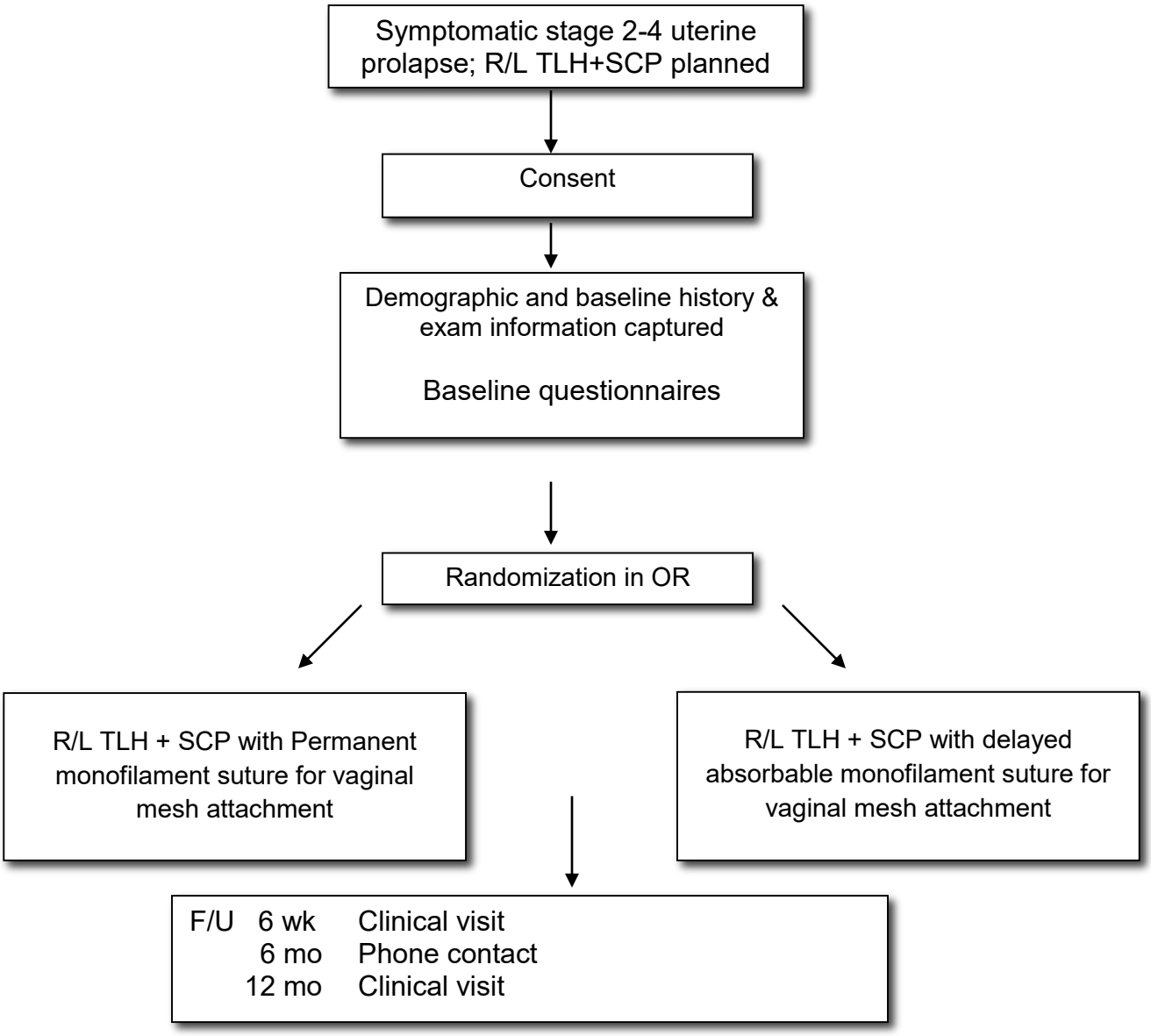
All participants who have completed the study surgery will proceed to be followed through the above-outlined study visits to Year 1 where the primary endpoint analysis will be achieved when the last per protocol subject completes this visit. All participants completing the Year 1 visit will be considered to have completed the study.

The data collection schedule of the trial is depicted in Table 1. Flow through the trial is depicted in Figure 1.

Table 1. Data Collection Schedule

	Baseline Visit	**Surgery (≤ 3 mo from BL Visit)**	**Week 6 Visit (-2 weeks/+4 weeks)**	**Month 6 Call (±4 weeks)**	**Year 1 Visit (±4 weeks)**
Informed Consent	X				
Medical & Surgical History Form	X				
POP-Q Exam	X		X		X
Vaginal examination (speculum and digital)			X		X
PFIQ-sf7, PISQ-IR, PFDI-sf20 questionnaires	X				X
Assessment of pain and analgesic use	X		X	X	X
Contact information update			X	X	
Surgical Procedure Form		X			
Assessment of Adverse Events		X	X	X	X
End of Study Form					X

Figure 1. Trial Flow



This protocol will adhere to the CONSORT guidelines for performing and reporting randomized controlled trials.[28] Women who are eligible but decline enrollment will be characterized in a manner consistent with the CONSORT requirements.

STUDY POPULATION

Inclusion Criteria

The study will include women with symptomatic uterovaginal POP, who have completed childbearing, are seeking surgical management, and are willing to proceed with placement of abdominal mesh.

1. Age ≥18
2. Subject must have apical with anterior or posterior vaginal prolapse with leading edge of prolapse to or beyond the hymen (C ≥ - (TVL / 2) AND Ba or Bp ≥ 0 by the POP-Q)
3. Subject reports a bothersome bulge they can see or feel per PFDI-20, question 3, response of 2 or higher (i.e., responses of “somewhat”, “moderately”, or “quite a bit”)
4. Eligible for robotic or laparoscopic sacral colpopexy
5. Desires surgical treatment for primary, symptomatic uterovaginal prolapse
6. English speaking
7. Willing to undergo hysterectomy

Exclusion Criteria

1. Patients who had prior hysterectomy
2. Patients who are not surgical candidates due to medical comorbidities
3. Current foreign body complications (including but not limited to erosion, fistula, abscess), and covering foreign bodies of any type (e.g. synthetic and biologic including allograft, xenograft)
4. Desires uterine conservation
5. Inability to give informed consent or to complete the testing or data collection
6. Anticipated circumstances resulting in an inability to follow up (geographic relocation, etc).
7. Pregnant or intends to become pregnant
8. Active systemic infection including any gynecologic infection, untreated UTI or tissue necrosis
9. History of pelvic organ cancer (e.g. uterine, ovarian, bladder, or cervical)
10. Prior or currently undergoing radiation, laser therapy, or chemotherapy in the pelvic area
11. Subject has taken systemic steroids (within the last month, steroid inhalers OK), or immunosuppressive or immunomodulatory treatment (within the last 3 months)
12. Systemic connective tissue disease (e.g. scleroderma, Marfan's syndrome, Ehlers Danhlos, collagenosis, polymyositis or polymyalgia rheumatic, lupus OK)
13. Chronic systemic pain that includes the pelvic area or chronic focal pain that involves the pelvis
14. Poorly controlled diabetes mellitus (DM), as indicated by Hemoglobin A1c > 9
15. Those requiring concomitant rectopexy
16. Subject is not able to conform to steep trendelenburg position
17. Known sensitivity to polypropylene

DATA COLLECTION & MANAGEMENT

Data collection will occur at each site per the schedule outlined in table 1. All study data will be recorded on CRFs by research staff and securely maintained at each site. CRFs shall be derived from source documentation and/or participant self-report. Any discrepancies between CRFs and source documentation shall be explained and documented on the CRF. Any changes

or corrections made to data on CRFs will be dated and initialed with a single line drawn through the incorrect entry and with the correct entry circled. Do not obscure the original entry.

Data will be entered by study staff at each site into a REDCap database that will be stored on a secure server by the Data Coordinating Center. Study data will be monitored by the Data Coordinating Center as outlined below under Study Monitoring and Documentation. All collected data must be entered into REDCap within 5 business days. Any queries to data entered into REDCap will be addressed by site staff within 5 business days. It is each site's responsibility to regularly check REDCap for data queries. See REDCap Data Entry Protocol for instructions on data entry and query resolution.

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 take measures to ensure that these essential documents are not accidentally damaged or destroyed.

OUTCOME MEASURES

Primary Outcome Measure

The primary outcome of this trial is the incidence of vaginal mesh and suture exposure rates related to the SCP mesh for both arms of the study through 1-year after surgery. Any suture or mesh visible in the vagina that is not at the position of a midurethral sling will be considered a positive outcome. Some participants may also undergo vaginal placement of a mesh sling for stress incontinence in a more distal vaginal location. Exposure of this mesh will not be considered a positive outcome for the primary outcome.

Secondary Outcome Measures

Secondary outcomes that we will measure include a composite of objective and subjective measures, self-reported outcomes, and assessment of complications as outlined below:

1. Assessment of efficacy at 1 year of each type of suture material using the composite cure as outlined below in a-d. Participants will be considered a surgical success for this composite outcome if each of the following four criteria are met:
    a) Anatomic success: Leading edge of the prolapse is at or above the hymen (POP-Q point Ba and Bp ≤ 0) and the vaginal apex descends less than 1/3 of the total vaginal length (C < - TVL/3)
    b) Subjective success: Patient denies symptoms of vaginal bulging per PFDI-20 question 3, answering "No" or "Yes" but "Not at All" bothersome (< 2)
    c) Assessment for re-intervention or re-surgery for recurrence or persistence of POP: No need for pessary use or additional surgical treatment for prolapse at any time after the initial procedure
    d) No mesh / suture exposure

2. Assessment of participant changes in QoL, symptom bother, and sexual functioning at 1 year compared to baseline[30,31]:
    - PFDI 20-Pelvic Floor Distress Inventory
    - PFIQ-7-Pelvic Floor Impact Questionnaire
    - PISQ-IR-Pelvic Organ Prolapse/Urinary Continence Sexual Questionnaire

3. Assessment of procedure-related or pelvic floor-related adverse outcomes in each group as classified according to the Clavien-Dindo surgical complication grading scale[29]. Adverse events will be assessed intra-operatively, at 6 weeks, 6 months, and 1 year postoperatively.

STATISTICAL CONSIDERATIONS

Statistical Methods

Data analyses will include t-tests for continuous data, chi-square or Fisher's exact for categorical data, and multi-variable regression to assess the effects of any bivariate analyses found to have a positive relationship. Confidence intervals will be reported for continuous data and will be included in the assessment and reporting of outcomes. When the data are analyzed, both chi square and Fisher's exact analyses are performed and the appropriate test and associated p value will be used based on the proportion of samples with input less than 5% of the total population. Those with a small output will utilize Fisher's exact.

The data will be analyzed as Intent to Treat. Missing data may occur if subjects fail to return for follow up, thus we plan to over-recruit in order to account for a 20% drop-out rate. Since study participants are undergoing surgery, they are more likely to return for their follow-up visits since these are part of their standard post-operative care. This will decrease the rate of drop-outs. The fact that this is an RCT will minimize the chance of a differential drop-out rate between the groups.

The rate of reported mesh exposure varies greatly from 0-27%, as discussed in our Background section on page 2 of the Investigator Protocol. Based on published data both at our institution and elsewhere in the literature, we determined that a 10% and 1% rate of mesh exposure in the two groups is both supported by data and clinically relevant, thus we are estimating a 9% difference in mesh erosion rates between the two groups: 1% vs 10%. This is a clinically significant difference that would affect a change in clinical practice.

Sample Size

The power calculation was performed using the statistical computation software Epi Info™ 7.1.3.10, developed on 3/11/14. It is a trademark of the Centers for Disease Control and Prevention and uses chi square for its computation of sample size for studies based on categorical data comparison such as the current study.

We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the mesh exposure rate among controls is 10%. If the mesh exposure rate for experimental subjects is 1%, we will need to study 80 experimental subjects and 80 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with the test of this null hypothesis is 0.1. The alpha of 0.1 is based on a one-sided hypothesis, estimating that mesh exposure rates will be higher in the study arm using permanent suture compared to the study arm using absorbable suture. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. We plan to enroll a total 200 subjects across sites to account for up to 20% loss to follow up, thus the use of chi square is appropriate given the adequately large sample size.

We feel the sample size is appropriate based on our sample size calculation, taking into account the estimated rates of mesh exposure in the two groups, as well as our clinical judgment of the number of procedures that are performed each year at the study sites. In the past year each

study site has performed 50 cases, for a total of 200 cases at all combined sites. Therefore our sample size of 100 subjects per study arm is feasible for completion in the time allotted.

Primary Hypothesis

Statistical testing will be performed to determine if the incidence of mesh and suture exposure in the absorbable suture arm is non-inferior to the permanent suture arm. The null hypothesis is that the incidence of mesh and suture exposure in the absorbable suture arm will be equal to the incidence of mesh and suture exposure in the permanent suture arm.

Secondary Hypotheses

1. Statistical testing will be performed to determine if the composite success rate in the absorbable suture arm will be non-inferior to the permanent suture arm. The null hypothesis is that the success rate in the absorbable suture arm is less than or equal to the success rate in the permanent suture arm.
2. Statistical testing will be performed to determine if the symptomatic success rate in the absorbable suture arm is non-inferior to the permanent suture arm. The null hypothesis is that the success rate in the absorbable suture arm is less than or equal to the success rate in the permanent suture arm.
3. Statistical testing will be performed to determine if the AE incidences rate of the absorbable suture arm is non-inferior to the permanent suture arm. The null hypothesis is that the AE incidences rate in the absorbable suture arm is greater than or equal to the rate in the permanent suture arm.

STUDY MONITORING AND DOCUMENTATION

The Principle Investigator 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. Appropriate approvals (e.g., IRB) of the revised protocol must be obtained prior to implementation at each site.

Site Documentation

All study documents included in this protocol that will be presented to subjects will be submitted to the IRB for approval. Each site will maintain a site study binder that will include the following:

- Enrollment log of patients who have consented to be in the study (electronic version)
- Protocol Deviation Log (electronic version)
- Adverse Event Log (electronic version)
- Investigator protocol and amendments
- IRB submissions, modifications, renewals
- Data Coordinating Center monitoring correspondence
- DSMB reports
- IRB approved Informed Consent Form
- All CRFs: Participant Contact Form, Inclusion/Exclusion Form, Medical & Surgical History Form, Baseline and Follow-Up Visit Forms, Surgical Procedure Form, questionnaires, AE Form, End of Study Form, Protocol Deviation Form

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, GCPs, and applicable regulations. By verifying compliance, 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 monitor and assess continued compliance with the protocol. Study data will be verified for roughly 25% of each site's overall data collection efforts. Site Investigators and study personnel must guarantee access to copies of source documents including medical records and auxiliary source documents for monitoring. Requests for de-identified supporting source documents from each site will be supplied via email within 10 days of the request.

Other monitoring activities include reviewing Informed Consent/Research Authorization Forms, assessing protocol compliance, regulatory and GCP compliance, reviewing changes to study personnel, verifying efforts made to locate "lost-to-follow-up" patients, and assessing other study-related functions that contribute to patient safety and study data integrity.

In the event of a Regulatory Inspection, sites should immediately contact UNC-CH. The Data Coordinating Center will manage the REDCap database, as well as monitor quality assurance for data entered by each site. Any data queries generated in REDCap by the Data Coordinating Center must be resolved by each site within 5 business days.

Protocol Deviations

Protocol deviations must be documented on the Protocol Deviation CRF, logged in each site's Protocol Deviation Log, and entered into RedCAP. This form will be completed for each protocol deviation related to any portion of the study timeline. An event number will be assigned by each site and recorded on the CRF according to each site's Protocol Deviation Log numbering order.

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

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, or per prevailing local requirements, 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) comprised of 2 external physicians (Dr. Karen Noblett and Dr. Michael Flynn) will review all adverse events (AEs) that occur across sites. A semi-annual report of all AEs will be generated and sent to the DSMB every 6 months.

All Serious Adverse Events (SAEs) will be reported to the study DSMB via email within 2 business days of site staff being informed of its occurrence. The PI and study coordinator will be cc'd on all communications between study sites and the DSMB. Copies of de-identified source documentation regarding the SAE will be included in the email, as well as a copy of the Adverse Event Form. Source documentation may include the operative/clinic note, Investigator/surgeon correspondence regarding the SAE, the original CRF, or other meaningful clinical information. Any request for additional documentation to determine relatedness to the operative procedures or pelvic floor will be honored within 5 business days.

Study PI: camatthe@wakehealth.edu
Project Manager: brupp@med.unc.edu
DSMB: Dr. Karen Noblett, knoblett@medsch.ucr.edu
DSMB: Dr. Michael Flynn, Michael.Flynn@umassmemorial.org

The PI (Matthews) will be responsible for ensuring that all sites comply with DSMB requests. The DSMB will then provide a written evaluation of each SAE detailing a judgment as to whether or not the event was deemed to be study related and a judgment as to whether, based on the review of the event, the study can:

1. Continue unchanged
2. Continue with recommended changes
3. Be stopped

The DSMB, PI, and each site will keep copies of all relevant information and committee decisions.

Criteria for Study Termination

After 50% of all study subjects have presented for the 6-week post-operative check, the overall rate of mesh and suture exposure will be calculated. If this rate is >12%, the study will be terminated. A second stopping parameter will be a difference in erosion rates between the two groups of >50%.

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 AEs must be recorded on the AE CRF, entered into the site AE log, then entered into REDCap. An event number will be assigned by each site and recorded on the CRF according to the number of AEs reported per patient. Each site investigator will determine the relationship of the AE to the operative procedures, the relationship of the AE to the pelvic floor, and the severity of each reportable AE.

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

Reportable AEs include those determined to be related to the operative procedures or pelvic floor. AEs not related to the operative procedures or pelvic floor will not be collected. Operative procedures include the following: Hysterectomy, sacrocolpopexy, sling, anterior and posterior vaginal repairs.

Please note that underlying diseases are not reportable AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but as an outcome of a specific SAE. If an AE has not resolved at the time of AE Form completion, save form as incomplete in REDCap until resolved. Once resolved, complete item 22 on 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.

Relationship to Pelvic Floor

Unrelated: No evidence that the AE has a relationship to the pelvic floor and supporting tissues

Related: If any of the following are met

- The AE is determined to be potentially related to the pelvic floor and supporting tissues including but not limited to lacerations, avulsions, tears, pelvic organ prolapse (cystocele, rectocele, enterocele, uterine, rectal), urinary incontinence (stress, urge), urinary voiding dysfunction (retention, obstructed voiding, incomplete emptying), fecal incontinence (urgency, irritable bowel syndrome), defecatory dysfunction (constipation, obstipation, stool trapping, IBS), pain (dyspareunia, pelvic, perineal), and infection (bladder, urinary tract, vaginal)
- There is a strong relationship to the pelvic floor and supporting tissues, and another etiology is unlikely
- There is no other reasonable medical explanation for the 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.

References

1. Wu JM, Matthews CA, Conover MM, Pate V, Jonsson Funk M. Lifetime Risk of Stress Urinary Incontinence or Pelvic Organ Prolapse Surgery. *Obstet Gynecol.* May 6 2014.
2. Smith FJ, Holman CD, Moorin RE, Tsokos N. Lifetime risk of undergoing surgery for pelvic organ prolapse. *Obstet Gynecol.* Nov 2010;116(5):1096-1100.
3. Barber MD, Brubaker L, Burgio KL, et al. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. *Jama.* Mar 12 2014;311(10):1023-1034.
4. Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. *Obstet Gynecol.* Feb 2009;113(2 Pt 1):367-373.
5. Nygaard I, Brubaker L, Zyczynski HM, et al. Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. *Jama.* May 15 2013;309(19):2016-2024.
6. Nygaard IE, McCreery R, Brubaker L, et al. Abdominal sacrocolpopexy: a comprehensive review. *Obstet Gynecol.* Oct 2004;104(4):805-823.
7. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. *Cochrane Database Syst Rev.* 2013;4:CD004014.
8. Geller EJ, Siddiqui NY, Wu JM, Visco AG. Short-term outcomes of robotic sacrocolpopexy compared with abdominal sacrocolpopexy. *Obstet Gynecol.* Dec 2008;112(6):1201-1206.
9. Paraiso MF, Walters MD, Rackley RR, Melek S, Hugney C. Laparoscopic and abdominal sacral colpopexies: a comparative cohort study. *Am J Obstet Gynecol.* May 2005;192(5):1752-1758.
10. Matthews CA, Carroll A, Hill A, Ramakrishnan V, Gill EJ. Prospective evaluation of surgical outcomes of robot-assisted sacrocolpopexy and sacrocervicopexy for the management of apical pelvic support defects. *South Med J.* May 2012;105(5):274-278.
11. Nosti PA, Umoh Andy U, Kane S, et al. Outcomes of abdominal and minimally invasive sacrocolpopexy: a retrospective cohort study. *Female Pelvic Med Reconstr Surg.* Jan-Feb 2014;20(1):33-37.
12. Osmundsen BC, Clark A, Goldsmith C, et al. Mesh erosion in robotic sacrocolpopexy. *Female Pelvic Med Reconstr Surg.* Mar-Apr 2012;18(2):86-88.
13. Hill AJ, Carroll AW, Matthews CA. Unanticipated uterine pathologic finding after morcellation during robotic-assisted supracervical hysterectomy and cervicosacropexy for uterine prolapse. *Female Pelvic Med Reconstr Surg.* Mar-Apr 2014;20(2):113-115.
14. Borahay MA, Oge T, Walsh TM, Patel PR, Rodriguez AM, Kilic GS. Outcomes of robotic sacrocolpopexy using barbed delayed absorbable sutures. *J Minim Invasive Gynecol.* May-Jun 2014;21(3):412-416.
15. Culligan PJ, Murphy M, Blackwell L, Hammons G, Graham C, Heit MH. Long-term success of abdominal sacral colpopexy using synthetic mesh. *Am J Obstet Gynecol.* Dec 2002;187(6):1473-1480; discussion 1481-1472.
16. Serati M, Bogani G, Sorice P, et al. Robot-assisted Sacrocolpopexy for Pelvic Organ Prolapse: A Systematic Review and Meta-analysis of Comparative Studies. *Eur Urol.* Mar 6 2014.
17. Visco AG, Weidner AC, Barber MD, et al. Vaginal mesh erosion after abdominal sacral colpopexy. *Am J Obstet Gynecol.* Feb 2001;184(3):297-302.
18. Cundiff GW, Varner E, Visco AG, et al. Risk factors for mesh/suture erosion following sacral colpopexy. *Am J Obstet Gynecol.* Dec 2008;199(6):688 e681-685.
19. Akyol A, Akca A, Ulker V, et al. Additional surgical risk factors and patient characteristics for mesh erosion after abdominal sacrocolpopexy. *J Obstet Gynaecol Res.* May 2014;40(5):1368-1374.
20. Bensinger G, Lind L, Lesser M, Guess M, Winkler HA. Abdominal sacral suspensions: analysis of complications using permanent mesh. *Am J Obstet Gynecol.* Dec 2005;193(6):2094-2098.

21. Stepanian AA, Miklos JR, Moore RD, Mattox TF. Risk of mesh extrusion and other mesh-related complications after laparoscopic sacral colpopexy with or without concurrent laparoscopic-assisted vaginal hysterectomy: experience of 402 patients. *J Minim Invasive Gynecol.* Mar-Apr 2008;15(2):188-196.
22. Brizzolara S, Pillai-Allen A. Risk of mesh erosion with sacral colpopexy and concurrent hysterectomy. *Obstet Gynecol.* Aug 2003;102(2):306-310.
23. Nosti PA, Lowman JK, Zollinger TW, Hale DS, Woodman PJ. Risk of mesh erosion after abdominal sacral colpoperineopexy with concomitant hysterectomy. *Am J Obstet Gynecol.* Nov 2009;201(5):541 e541-544.
24. Geller EJ, Parnell BA, Dunivan GC. Robotic vs abdominal sacrocolpopexy: 44-month pelvic floor outcomes. *Urology.* Mar 2012;79(3):532-536.
25. Shepherd JP, Higdon HL, 3rd, Stanford EJ, Mattox TF. Effect of suture selection on the rate of suture or mesh erosion and surgery failure in abdominal sacrocolpopexy. *Female Pelvic Med Reconstr Surg.* Jul 2010;16(4):229-233.
26. Marinkovic SP. Will hysterectomy at the time of sacrocolpopexy increase the rate of polypropylene mesh erosion? *Int Urogynecol J Pelvic Floor Dysfunct.* Feb 2008;19(2):199-203.
27. Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol.* Jul 1996;175(1):10-17.
28. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med.* Jun 1 2010;152(11):726-732.
29. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* Aug 2009;250(2):187-196.
30. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). *Am J Obstet Gynecol.* Jul 2005;193(1):103-113.
31. Rogers RG, Coates KW, Kammerer-Doak D, Khalsa S, Qualls C. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). *Int Urogynecol J Pelvic Floor Dysfunct.* Aug 2003;14(3):164-168; discussion 168.