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Design of a Three-Arm Randomized Trial for Post-Hysterectomy Vault Prolapse involving Sacral Colpopexy, Transvaginal Mesh and Native Tissue Apical Repair: the Apical Suspension Repair for Vault Prolapse In a Three-Arm Randomized Trial (ASPIRe)

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Abstract

Objective—To present the design of the Apical Suspension Repair for Vault Prolapse in a Three-Arm Randomized Trial (ASPIRe) which compares the efficacy and safety of three apical repairs: native tissue transvaginal repair, transvaginal mesh, and sacral colpopexy.

Methods—Patient selection criteria, primary and secondary outcome measures including patient-reported outcome questionnaires, masking, surgeon certification, procedure standardization, adverse events collection and adjudication, and cost analysis will be described for this multi-centered randomized trial. Given the unique risks/ benefits of each technique, a non-inferiority design will be used to compare apical transvaginal mesh to mesh sacral colpopexy. A superiority design will be used to compare the two mesh repairs to native tissue transvaginal apical repair. Survival analysis will be used to assess a composite primary outcome for success composed of a subjective measure (no prolapse symptoms), objective measure (no prolapse beyond the hymen) and no prolapse retreatment, with a minimum follow up of 36 months. Secondary outcome measures collected every 6 months include assessment of validated general and condition-specific quality of life measures, global impression of improvement, satisfaction and regret, body image, and sexual function.

Results—Randomization and surgical treatment of 360 participants is complete and the study is in the follow-up phase.

Conclusions—This report will provide valuable insight on the design of a novel 3-arm surgical trial utilizing mesh versus native tissue to repair vaginal vault prolapse. This trial will provide level 1 evidence on the risks and benefits of mesh augmented versus native tissue apical repairs.

Keywords

pelvic organ prolapse; vaginal vault prolapse; sacrospinous ligament suspension; transvaginal mesh; sacral colpopexy; randomized controlled trial

Introduction

After conservative treatment fails or is declined, many women consider surgical management for pelvic organ prolapse (POP). Post-hysterectomy apical vaginal vault prolapse (VVP) can be surgically managed with a variety of techniques and approaches ranging from transvaginal obliterative procedures to transvaginal or transabdominal reconstructive procedures with or without the use of biologic grafts or synthetic mesh. Native tissue (NT) apical vaginal repairs including sacrospinous ligament suspension (SSLS) and uterosacral ligament suspension (USLS) have demonstrated adequate reliability for improving subjective symptoms, however many pelvic reconstructive surgeons have concerns about procedural durability, acceptable success rates with advanced prolapse, and recurrence of anterior and/or posterior compartment prolapse.

Native tissue (NT) transvaginal repairs have uncommon complications including ureteral injury, foreshortened vagina, or restriction of the vaginal caliber.^{1,2} Transvaginal mesh (TVM) repairs are associated with improved anatomic success rates in the anterior compartment compared to NT repairs, but there are concerns regarding risks of vaginal pain,

reoperation for mesh exposure, and lack of evidence that mesh results in better subjective outcomes.^{2,3} In 2012, the Food and Drug Administration (FDA) issued post-market surveillance study orders for companies making transvaginal mesh kits for prolapse citing concerns with safety and efficacy. Following the FDA announcement, TVM techniques evolved to use lighter weight mesh, less material to decrease mesh load, trocar-free techniques, and alterations in incision location with deeper dissection planes. Published reports in 2011–2012 suggest that complication rates for TVM procedures had declined to an average of 5% (ranging from 1.5% – 17% across studies), with reoperation rates < 13%, and anatomic and comparable subjective success rates > 90%.⁴ These short-term results are encouraging, but longer-term results (> 36 months) are needed to consider the relative risks and benefits of these procedures. The need for longer term results has become more critical since the implementation of this trial in February 2016 given the FDA's reclassification of TVM kits to class III in 2016 and the requirement for manufacturers to submit premarket approval applications. In April 2019, the lack of the 36 month safety and efficacy data comparing TVM to NT repairs resulted in the FDA ordering a halt to the sale and distribution of TVM kits within the United States.⁵

Sacral colpopexy (SC) utilizing mesh has been considered the most durable procedure for VVP with comparable short-term success rates demonstrated for open, laparoscopic and robotic approaches.^{6–8} Over 300 published reports and systematic reviews cite low rates of mesh erosion (<5%) and dyspareunia (<5%) and high rates of short term success (90–95%).¹ Compared to vaginal approaches, SC procedures have longer operative times, higher associated costs, and more potential major adverse events (bowel injury, post-operative bowel obstruction, and sacral osteomyelitis) given that intraperitoneal access is required.^{9,10} Long-term outcomes beyond seven years are less encouraging with reports of mesh erosion rates of up to 10% and prolapse recurrence rates of 24–48%, depending on the definition of failure.¹¹

The ASPIRe trial design including selection criteria, primary and secondary outcomes, study measures, standardization, and evaluation of unique design and exploratory outcome measures will be described.

Methods

Study Design

The ASPIRe trial is being conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)-sponsored Pelvic Floor Disorders Network (PFDN). The primary aims of this study are to determine if TVM is non-inferior to mesh SC for correction of post-hysterectomy VVP and to decide if mesh-reinforced repairs performed by abdominal or vaginal approaches are superior to NT vaginal repair. If TVM is found non-inferior to SC, the superiority of TVM to SC will also be determined. Participants were randomized to one of the three surgical treatments for VVP. The hypothesis is two-fold: (1) treatment success with vaginally placed mesh is non-inferior compared to abdominally placed mesh for VVP, with a hazard ratio of failure no higher than 1.93 and (2) mesh repairs (regardless of route) are superior to NT apical vaginal suspension. The primary outcome, which will be measured at a minimum of 36 months and a maximum of 60 months, is time

until treatment failure utilizing a composite outcome comprised of objective (prolapse past the hymen), subjective (bothersome bulge symptoms based on Question 3 of the Pelvic Floor Distress Inventory (PFDI-20))¹², or prolapse retreatment using a survival analysis.

Secondary outcomes are comprised of anatomic and functional measures obtained through patient -reported outcome (PRO) questionnaires, including prolapse, urinary, bowel, sexual, body image, and health related quality of life. Given concerns with synthetic mesh safety, adverse events, pain and complications related to mesh and sutures are reported. Objective measures using the pelvic organ prolapse quantification (POP-Q) system will be obtained at 6-month intervals for 5 years. While the leading edge of prolapse is used definition of objective success, POP-Q points Ba, Bp, and C will be compared across all groups. The study will assess multiple baseline factors to characterize risk factors associated with failure. Given the additional costs of mesh and variation in operative times, the study will also include a cost effectiveness analysis to evaluate cost of care relative to gains in health utilities and quality of life. ASPIRe was registered with [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02676973) (NCT02676973) prior to patient enrollment.

Study Population

Adult women (>21 years) with symptomatic post-hysterectomy vaginal vault (apical) prolapse beyond the hymen and with the vaginal vault (apex) descending into at least the lower two thirds of the vagina were eligible for participation if they desired surgical management. To be included, women must have indicated a 'sensation of bulging' or 'something falling out' on Question 3 of the PFDI-20.¹² Table 1 provides the inclusion and exclusion criteria of this study. A subset of the participants who are ≥ 65 years of age will undergo preoperative frailty and mobility assessments.¹³ This protocol adheres to the Consolidation Standards of Reporting Trials (CONSORT) guidelines for performing and reporting randomized controlled trials.¹⁴ Women who were eligible but declined enrollment will be characterized consistent with the CONSORT requirements.

Baseline Assessments

Once eligibility was confirmed, baseline information was obtained and include demographics (age, race/ethnicity, marital status, education), medical history (obstetric history, prior POP or urinary incontinence treatment, estrogen status, smoking history, diabetes mellitus diagnosis, previous urinary tract infection, current medication use), physical examination (height, weight, POP-Q measurements), and PRO measures as noted in the timeline outlined in Table 2.

Randomization

After participant eligibility was determined and consent obtained, randomization was performed with the goal to schedule surgery within 6 weeks. Randomization in the operating room was not feasible because of the unique equipment and availability necessary to perform minimally invasive SC.

Randomization occurred in a ratio of 1:1:1 for each treatment arm. This was performed using a permuted blocks block size known only to the Data Coordinating Center (DCC) and

stratified by site and age category (<65 and ≥65). For each participant, the web-based system determined the treatment allocation from a static randomization table developed by the study randomization statistician prior to the start of the study. Only the study statistician and randomization system programmer had access to the randomization table, thereby minimizing the risk of selection bias. In response to the April 16, 2019 FDA order to halt the sale and distribution of TVM within the United States, study enrollment was stopped within a few patients of completion and the protocol was amended to halt randomization into the TVM arm. At the time, 18 enrolled participants were awaiting surgery. Those remaining patients that had been randomized to TVM were re-randomized to receive either SC or NT in a 1:1 ratio.

Study Masking/ Unmasking

Participants were masked to the allocated treatment approach until completion of surgery. Participant masking after surgery was not feasible because participants receiving SC will have abdominal incisions. Although participants were unmasked after surgery, bias in assessing the objective portion of the primary outcome was minimized, by having masked, non-surgeons investigators examine and determine the POP-Q measures and identify complications.

Surgeon Certification and Standardization of the Surgical Procedures

All ASPIRe study surgeons were board-eligible or certified in Female Pelvic Medicine & Reconstructive Surgery and were experienced with all three approaches, having conducted a prerequisite minimum number of cases for each procedure. Certification criteria ensured that all study surgeries were performed by surgeons who were trained on each procedure to assure study validity, while at the same time establishing standards for the trial that will allow the results to be generalized to other surgeons. Certification requirements are outlined in Table 3. Trainees were incorporated into surgical cases as per the local guidelines at each clinical site.

The NT arm of the trial allowed for either a USLS or SSLS procedure, thereby providing generalizability across study sites. Based on the OPTIMAL trial, these procedures demonstrated similar outcomes.^{2,15} The techniques for both have been previously described.¹⁶

For the apical TVM arm, the Uphold Lite® (Boston Scientific, Marlborough, MA) was utilized given prior PFDN experience with this technique/device in a previous trial.¹⁷

The SC arm permitted either open, laparoscopic or robotic approaches. The use of any SC approach improved generalizability; however, essential portions of the procedure were standardized in the trial. All procedures are illustrated in Figures 1,2 and 3 with standardized techniques outlined in Table 4. If during the randomized surgery the surgeon encountered anatomic findings which prevented the safe completion of that procedure, the surgeon selected between the other two study surgeries.

Other operative rules included: 1) cystoscopy with assessment of ureteral efflux was required after completion of the vault suspension. 2) All concomitant, non-index surgical

procedures (planned and unplanned) were recorded. The surgeon had the discretion to alter the preoperative plan to achieve the desired anatomic result with such alterations being recorded. 3) Anterior and posterior colporrhaphies were performed at the discretion of the operating surgeon such that points Ba and Bp were –1 cm at the end of the procedure. Colporrhaphies were performed using either 2–0 or 0 delayed absorbable sutures. 4) Full-length mid-urethral slings (MUS)—either transobturator or retropubic—were used in all study groups per - surgeon discretion.

Because MUS have not been shown to provide additional distal anterior vaginal wall support for patients undergoing laparoscopic SC, they were chosen so as not to influence the primary outcome.¹⁸ In contrast, an association with increased anatomic prolapse failures was identified in women undergoing retropubic urethropexy.¹⁹ Thus, full-length MUS were the preferred intervention to address stress urinary incontinence.

Other measures—Intraoperative measures/events including mean operative time, estimated blood loss, blood transfusion, intra-operative complications by organ system and any additional treatment related to an adverse event (AE) was collected. Intra-operative and immediate postoperative adverse events were recorded by the surgeon and categorized using a modified Dindo Classification.

At follow-up visits, instruments assessing the primary and secondary outcomes will be administered as outlined in Tables # 2 and 5. A physical examination by a masked non-surgeon will be performed to assess anatomic outcomes, and to evaluate for mesh exposures and erosions. The presence of other AEs will be determined by directed questioning, PRO questionnaires, and chart review. Specific guidelines for AE data collection can be found in Table #6. AEs that occur during the study period will be recorded on case report forms. Failure of the study interventions to adequately treat prolapse based on the composite definition of failure, new onset stress and urgency urinary incontinence and fecal incontinence will be captured by PRO endpoint measures and will not be recorded as an AE. While the objective and subjective definition of failure is based on specific points, the decision for re-treatment with either pessary or repeat prolapse surgery will be by shared decision making between the patient and her surgeon. An AE adjudication committee, masked to clinical site, will provide oversight on consistency of collection and designation of AEs.

Economic Evaluation and Analysis—A cost-effectiveness analysis will be conducted from a health care sector perspective, and the analysis will be expressed as incremental cost required to produce one additional unit of quality-adjusted life year (QALY). QALYs will be calculated from the SF-6D preference-based utility index algorithm derived from the SF-12 instrument.²⁰ Data on each participant's use of medical and non-medical resources will be collected during the follow-up period.

Additional Exploratory Aim: Global Composite Outcome—Success, failure, and AEs may be defined differently by surgeons and patients based upon goals and expectations. It is critical to measure patient perspective and to assess how complications and negative outcomes are interpreted and valued by patients. Currently, the impact of AEs on patients'

perception of surgical success and failure regarding POP is not known. The Decision Regret Scale (DRS) and Satisfaction with Decision Scale (SDS) are patient-centered outcome measures that have demonstrated good psychometric properties in numerous patient populations and they have been adapted and validated for pelvic floor disorders (DRS-PFD and SDS-PFD).^{21–23}

An exploratory aim of this trial will be to evaluate the use of patient centered outcomes using DRS-PFD and SDS-PFD, utility scales (SF-6D), PGI-I, and AEs to determine if a valid and reliable patient centered global composite outcome can be developed to reliably evaluate these important factors.

STATISTICAL DESIGN

Sample Size/Power Calculations

Sample size calculations were generated under the assumptions that the study would have an overall Type I error rate of 0.05, utilizing a randomization ratio of 1:1:1, and that the Type I error (alpha) would be distributed among the following three hypotheses: 1) apical TVM is non-inferior to mesh SC (alpha 0.03); 2) SC is superior to native tissue repair (alpha 0.01); 3) apical TVM repair is superior to NT apical repair (alpha 0.01). The sample size estimates also assumed that the primary analyses will be based on a survival analysis model with a 2-year recruitment period and a follow-up period with a minimum of 3 years and a maximum of 5 years; that lost to follow-up on each arm will be no more than 5% per year; that the 2-year success rates for SC and TVM repair will be 80%; and that the 2-year success rate for NT will be 60%. These 2-year success rates represent hazards of 0.1116 and 0.2554, respectively, under the assumption that the failures follow an exponential survival model. For the non-inferiority hypothesis, analyses assume a two-year 15% margin; this non-inferiority margin corresponds to a hazard ratio of 1.93.

Based on these assumptions, the hypothesis test requiring the largest number of participants, that will determine the overall study sample size, is the evaluation of non-inferiority regarding TVM versus SC. A sample size of 121 participants per arm will provide 85% power to demonstrate non-inferiority. Assuming that 121 participants will be randomized to NT repair, the overall sample size of 363 participants will provide > 93% power to demonstrate that each of the mesh augmented arms is superior to native tissue repair. Because randomization occurred prior to scheduling the surgery, some randomized participants did not receive surgery as a consequence of patient-related events occurring after randomization. To maintain planned power, randomization was to be continued until a total of 363 patients were randomized and treated. Because of the FDA order regarding TVM, enrollment was stopped, resulting in a final sample size of 360 randomized and treated participants. The design modification excluding TVM for the last 18 participants is expected to have minimal impact on the planned statistical power, while the actual recruitment period of 36 months increases the power.

Data Analysis

Although participants will be followed up to 5 years, the primary analysis is scheduled to occur after the last treated participant has completed 3 years of follow-up. Primary statistical evaluations for superiority will follow a modified intent-to-treat approach and this will exclude participants who were randomized but never received surgery due to patient-specific reasons unrelated to the randomized treatment. Primary evaluations of non-inferiority will follow a per-protocol approach, and this will further exclude all participants with a major protocol violation related to the index surgery such as receiving a surgery other than what was intended with randomization. AE rates will be evaluated for all randomized participants who received one of the three study surgeries, and they will be grouped by the surgery actually received.

Composite failure rates will be compared using interval censored piecewise proportional hazards survival analysis. For each analysis population, a single model will be used to generate four hypothesis tests. The first test will compare the hazard ratio of the TVM to the SC arm against the hypothesized non-inferiority margin of 1.93 (using a 1-sided test of alpha 0.03), followed by a test of superiority if non-inferiority is shown (using a 2-sided test of alpha 0.03). The other two hypothesis tests will compare the hazard ratio of TVM and SC, respectively, to NT repair against the hypothesized null ratio of 1.0 (using 2-sided tests of alpha 0.01). All model-based analyses will include terms for site and age category (<65 and 65) stratification parameters used in the randomization.

Treatment groups will be compared for secondary efficacy measures collected across visits using linear mixed models for continuous outcomes and generalized linear models for binary measures, and this will account for missing data due to differential follow-up time associated with the primary design. Details of all planned analyses will be documented in a statistical analysis plan prior to database lock.

Unique Study Design Issues

Similar to the SUPeR trial, potential physician and patient bias against TVM, with the potential perception of commercial bias were taken into account.²⁴ Regarding the general considerations and rationale for designing and performing clinical trials that evaluate TVM, we refer readers to the SUPeR methods paper which provides this reasoning.²⁴ Considerations specific to ASPIRe are discussed below.

Physician preference against transvaginal mesh—At the time of study development, surveys indicated that many urogynecologists were still performing mesh augmented vaginal procedures, and this demonstrated continued relevance of the ASPIRe trial. All participants in ASPIRe had prior pelvic surgery and it is anticipated that many will have had prior POP surgery. The use of mesh for recurrent symptomatic prolapse is commonly accepted by physicians and professional organizations compared to the use of TVM for primary prolapse operations.

Participant bias—It was thought that evidence-based counseling regarding the risks and benefits of the three commonly performed surgical options offered in this trial, without an

emphasis on identifying which surgery is “best”, will help assuage potential patient bias. In addition, it was thought that patients with VVP will have less bias than the general population, especially if they had prior POP surgery, since many patients in clinical practice elect for mesh augmented repairs to treat recurrent POP.

Perception of commercial bias—In this trial, no external industry funding was sought or utilized. At the time of this trial, Uphold LITE was the only commercially available TVM “kit” available.

FDA announcements related to transvaginal mesh—At the time of development of this trial, there was a need to collect high-quality information related to TVM for prolapse and the PFDN responded by including a TVM arm in the ASPIRe trial. As this trial initiated enrollment in 2016, the FDA reclassified surgical mesh for transvaginal repair of pelvic organ prolapse into class III and required premarket approval (PMA) applications for manufacturers of TVM kits. This announcement increased the difficulty of enrolling participants into a randomized surgical trial, and this likely resulted in prolonged recruitment phase beyond the anticipated 2-year duration. In addition, prior to complete enrollment of the trial the FDA ordered all TVM manufacturers on April 16, 2019 to stop selling and distributing their products immediately.⁵ Given these events, the PFDN steering committee elected to halt the surgical randomization to the TVM arm. The PFDN was masked to the number of participants who were randomized to each arm of the study during this discussion.

Data and Safety Monitoring Board

The *Eunice Kennedy Shriver* NICHD has a Data Safety Monitoring Board (DSMB) to oversee this study. Members of the DSMB are independent of the study investigators and they include representatives within urology, urogynecology, and those with biostatistics expertise, and a lay member. The DSMB has regularly scheduled meetings. This protocol was approved by the DSMB prior to recruitment initiation. The DSMB monitors study progress and can recommend that the trial be stopped for safety. There were no plans to stop for either futility or efficacy.

Results

Participants were enrolled from February 28, 2016 to April 16, 2019 at 9 PFDN study sites. Randomization and surgical treatment of 360 participants is complete and the study is in the follow-up phase.

Discussion

Surgical correction of the vaginal apex at the time of a prolapse procedure is critical for optimizing all vaginal compartment anatomic outcomes.²⁵ The procedure associated with the best anatomical outcomes, lowest complication rates and highest patient satisfaction in women with VVP is unknown. To that end, a three-arm, multi-center, prospective, randomized trial was designed to compare the outcomes of three commonly performed procedure approaches used to treat VVP.

Native tissue repairs for VVP remain a commonly used surgical technique. The OPTIMAL study, a large randomized trial that evaluated two commonly performed NT surgeries that treat apical compartment prolapse, SSLS and USL, demonstrated similar anatomic success rates at 2 years and extended follow-up did not demonstrate statistically significant difference between the two techniques. As such, both apical NT techniques were allowed in this protocol.

With both the 2011 FDA warning and the associated escalation in litigation, some mesh manufactures removed vaginal mesh products from the market.^{2,15} Given both the recommendation by multiple professional organizations and the FDA regarding the need for further research on the outcomes of TVM procedures and the potential for mesh augmented repairs to improve outcomes compared to NT repairs, a TVM treatment arm was included. When the trial was initiated, there was only one commercially available apical TVM kit. A free hand synthetic mesh option was considered during trial design, but this option lacked standardization, network experience, and adequate safety and efficacy outcomes.

Sacral colpopexy has long been considered the gold standard for VVP.²⁶ However, the use of contemporary composite outcomes showing both higher rates of failure mesh exposure raise concern as to whether SC has the durability and long-term safety to be considered the gold standard operation for apical prolapse.¹¹

Approaches for SC range from open to laparoscopic to robotic. It is commonly accepted that all approaches result in similar long-term anatomic and subjective success rates. Although SC performed through a minimally invasive approach allows for direct comparisons of hospital stay and postoperative pain levels to vaginal approaches, there was concern that restricting the approach would impact recruitment by limiting the number of surgeons and thereby limiting generalizability.

While the use of synthetic mesh to reinforce apical prolapse repair is believed to reduce failure rates and improve durability, the potential for repeat surgical procedures for mesh related morbidity and increased surgical complexity must be weighed for these procedures. The current study considers all these factors with comprehensive collection of AEs, pain, body image and sexual function assessments at regular intervals.

There are unique issues of interest related to the current study design. In terms of characterizing the differences in outcome of the mesh arms, the use of one-sided testing using a non-inferiority approach provided a feasible sample size to allow the determination of whether TVM is non-inferior or inferior to SC for composite success, and whether TVM is superior to SC. The resulting sample size also provides a greater than 90% power to determine if each mesh arm outcome is superior to NT transvaginal repair.

Other important lessons were learned from designing the ASPIRe trial: 1) the three-arm design of the trial increased the complexity of the trial design and recruitment; however, it allowed the evaluation of three unique surgical approaches within a single surgical trial; 2) such trials likely require multi-center networks with established infrastructures and experienced investigators and 3) randomized surgical trials in which participants are initially

masked are difficult to perform and 4) flexibility in the range of surgical procedures performed in clinical practice improves surgeon acceptance.

The increased media attention and controversy on vaginal mesh and the and the FDA's reclassification of TVM could have made recruitment into this randomized trial more difficult, thereby prolonging the enrollment period; however, the acceptance of TVM for POP repair at the time of protocol development made including a TVM arm essential. Uncontrollable external factors including the FDA order to stop the sales and distribution of TVM that occurred near study completion required modification of the trial prior to completion of randomization.

A limitation of this trial included difficulty with recruitment into a three-arm trial. Because of the unique operative room requirements of SC, it was not feasible to randomize subjects in the operating room; however, study subjects were masked to their procedure until after it had been performed reducing the probability of patients dropping out prior to their surgical procedure. Given the allowed approaches (abdominal versus vaginal), the addition of sham incisions was not deemed appropriate for participants in the vaginal approach groups. Thus, postoperative masking of the participants was not a credible option. While this has the potential to increase bias towards or against mesh-based repairs on subjective outcomes, the personnel performing the physical examinations in follow-up were masked to the surgical procedures, thereby eliminating bias from objective assessments. The choice to halt enrollment into the TVM arm after the April 2019 FDA order may potentially impact study power of the study outcomes involving TVM. Yet, by designing the trial using a survival analysis with follow-up ranging from 36 to 60 months and increasing enrollment duration from 24 months to 36 months will likely off set the potential of not reaching the anticipated sample size in the TVM arm.

Strengths of this study include the ability to study three different approaches to apical VVP repair, thus allowing variation within each group and standardization of critical portions of each procedure. The three-arm study design affords a large randomized prospective surgical trial with a relatively long-term outcome instead of three individual clinical trials, thereby decreasing study costs and reducing the number of subjects required. This study involves only women with VVP allowing the evaluation of these differing approaches without the impact of hysterectomy on efficacy and safety of these procedures.

In summary, surgeries addressing the vaginal apex in women with VVP have unique advantages and risks. With women increasingly seeking care for this condition, there is a critical need for level 1 data describing pertinent objective and subjective outcomes and complications in a robust and unbiased manner.

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Figures 1–3:

Illustrations depicting the 3 apical approaches being compared in ASPIRe randomized trial.

1. Native Tissue Options: A. Sacrospinous Ligament Suspension and B. Uterosacral Ligament Suspension
2. Apical Transvaginal Mesh
3. Sacral Colpopexy

Table 1:**Inclusion and Exclusion Criteria in the ASPIRe Trial****Inclusion Criteria**

1. Women age 21 or older
2. Prior total hysterectomy (no cervix present)
3. Prolapse beyond the hymen (defined as Ba, C, or Bp > 0 cm)
4. Vaginal cuff descent into at least the lower two thirds of the vagina (defined as point C > -2/3 TVL)
5. Bothersome bulge symptoms as indicated on question 3 of the PFDI-20 form relating to 'sensation of bulging' or 'something falling out'
6. Desires surgical treatment for post-hysterectomy vaginal prolapse
7. Available for up to 60 month follow-up

Exclusion Criteria

1. Previous synthetic material or biologic grafts (placed vaginally or abdominally) to augment prolapse repair including anterior, posterior and/or apical compartments
2. Known previous formal SSLS performed for either uterovaginal or post-hysterectomy vaginal vault prolapse *
3. Known adverse reaction to synthetic mesh or biological grafts; these complications include but are not limited to erosion, fistula, or abscess
4. Unresolved active chronic pelvic pain
5. Prior abdominal or pelvic radiation
6. Contraindication to any of the index surgical procedures
 - a. Known Horseshoe Kidney or Pelvic Mass overlying the sacrum
 - b. Active diverticular abscess or diverticulitis
 - c. Shortened vaginal length (<6 cm TVL)

*** NOTE:**

- Mesh used for only mid-urethral sling will NOT be an exclusion.
- Only documented SSLS will be an exclusion.
- If prior POP repair is unknown and unable to be documented, subjects will be eligible based on clinician judgment.

SSLS, sacrospinous ligament suspension; TVL, total vaginal length

Table # 2:

Timeline of Events

MEASURE	SCREEN	BASELINE	PERIOP	6 WK -1 wk / +2wks	6M +/- 6wks	12 M +/- 6wks	18 M +/- 6wks	24 M +/- 6wks	30 M +/- 6wks	36 M +/- 6wks	42 M +/- 6wks	48 M +/- 6wks	54 M +/- 6wks	60 M +/- 6wks
Window (+/- wk)														
Eligibility/ Consent	X													
Demographics		X												
Medical History		X												
Randomization		X												
Physical Exam (height, weight and PVR)		X												
Surgeon's Report and Hospitalization			X											
POP-Q for Inclusion Criteria Unmasked Staff		X												
Study Surgery Status			X											
6 Week Unmasked Evaluator Assessment (includes Complications Assessment)				X										
6 Week Postoperative Recovery Assessment				X										
6-60 Month Masked Evaluator Assessment (includes POP-Q and Complications Assessment)					X	X	X	X	X	X	X	X	X	X
Retreatment and Complications Assessments Unmasked (6-60 month visit form)					X	X	X	X	X	X	X	X	X	X
AE Review			X	X	X	X	X	X	X	X	X	X	X	X
Exams for Mesh Exposure				X	X	X	X	X	X	X	X	X	X	X
Non-Pain Med Collection		X	X	X	X	X	X	X	X	X	X	X	X	X
Catheterization Follow-Up*														
Functional Activity Scale		X			X	X	X	X	X	X	X	X	X	X

Q 2 weeks if need for continuous catheterization post 6-Week Visit

MEASURE	SCREEN	BASELINE	PERIOP	6 WK -1 wk / +2wks	6M +/- 6wks	12 M +/- 6wks	18 M +/- 6wks	24 M +/- 6wks	30 M +/- 6wks	36 M +/- 6wks	42 M +/- 6wks	48 M +/- 6wks	54 M +/- 6wks	60 M +/- 6wks
Window (+/- wk)														
Surgical Pain Scale		X		X	X	X		X		X		X		X
Body Part Pain Score		X		X	X	X		X		X		X		X
PFDI-20 (includes POPDI-6, CRADI-8, UDI-6)		X			X	X		X		X		X		X
PFDI-20 Question 3 Only							X		X		X		X	
PFQ-7		X			X	X		X		X		X		X
PGI-I					X	X		X		X		X		X
PISQ-IR		X			X	X		X		X		X		X
BIPOP		X			X	X		X		X		X		X
SF-12		X			X	X		X		X		X		X
DRS-PFD/SDS-PFD						X		X		X				

Table 3.**Surgeon Certification for the Apical Procedures in ASPIRe Trial.**

FOR SACRAL COLPOPEXY CERTIFICATION:

1. All surgeons will review the written manual of operation illustrating the essential components of sacral colpopexy technique.
2. All certified surgeons should have performed a minimum of 20 sacral colpopexies by the approach they are performing; with at least 5 of these procedures in the 12 months prior to beginning participant enrollment.

FOR SSLS/USLS CERTIFICATION:

1. All surgeons will review the written manual of operation illustrating the essential components of SSLS and USLS technique.
2. All certified surgeons should have performed a minimum of 20 SSLS and/or USLS; with at least 5 of these procedures in the 12 months prior to beginning participant enrollment.

FOR APICAL TVM CERTIFICATION:

1. All surgeons will view a surgical DVD illustrating essential components of the Uphold Lite®
 2. All certified surgeons should have performed 20 sacrospinous ligament dissections in their careers with performance of at least 10 anterior vaginal dissections to the sacrospinous ligament
 3. Performance of at least 10 Capio suture applications
 4. Either performance of, or hands on proctoring of at least 5 Uphold Lite® procedures for uterovaginal prolapse or cuff-vaginal prolapse for the technique that he/she will be performing.
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SSLS, sacrospinous ligament suspension; USLS, uterosacral ligament suspension; TVM, Transvaginal Mesh

Table 4:**Standardization for the 4 approaches used in the ASPIRe Trial****Native Tissue with Sacrospinous Ligament Suspension (SSLs)**

1. SSLS is performed through a vaginal incision.
2. The 4 points on each vaginal wall (anterior, posterior and lateral on each side) that comfortably reaches the sacrospinous ligament yet eliminates sagging are identified. These points will serve as the fixation point for the suspension. The excess vagina in between these points is removed.
3. Two permanent and two delayed absorbable (4 sutures total), 0 or 2–0 monofilament stitches must be placed in the left OR right ligament. Bilateral procedures are not permissible.
4. One arm of each suture will be passed into the anterior and posterior fibromuscular wall of the vaginal apex, respectively (4 suture arms in the anterior edge and 4 suture arms in the posterior edge). The permanent sutures will be placed near full thickness, excluding vaginal epithelium. The delayed absorbable sutures will be placed full thickness through the vaginal wall with the knot tied inside the vaginal canal.
5. Permanent sutures will be placed so that the knots, when tied, are not exposed in the vaginal canal (“buried”). The use of a pulley stitch is allowed.
6. Other aspects of the procedure—such as management of enterocele—will be left to the surgeon’s discretion and will be recorded.

Native Tissue with Uterosacral Ligament Suspension (USLS):

1. USLS is performed through a vaginal incision.
2. One permanent and one delayed absorbable 0 or 2–0 monofilament suture (2 sutures per side; 4 sutures total) must be placed in each ligament, extending to the ipsilateral anterior and posterior fibromuscular wall of the vaginal apex. The permanent sutures will be placed near full thickness, excluding vaginal epithelium. The delayed absorbable sutures will be placed full thickness through the vaginal wall with the knot tied inside the vaginal canal.
3. No plication of the uterosacral ligaments across the midline or culdoplasty is allowed.
4. Other aspects of the procedure—such as management of enterocele—will be left to the surgeon’s discretion and will be recorded.
5. If clinical circumstances prohibit safe/effective completion of the planned procedure, the preferred back-up procedure is a SSLS as described above. In the event that both USLS and SSLS cannot be performed safely or effectively, the choice of vaginal suspension procedure will be left to the surgeon’s discretion and recorded.

Apical Transvaginal Mesh: Uphold Lite® Procedure

1. Hydrodissection of the vaginal walls will be performed with at least 30 cc of 0.25% bupivacaine with epinephrine or dilute Pitressin (20 Units/50–100 cc).
2. An approximate 4 cm transverse vaginal incision is made in the anterior vaginal wall between the bladder neck and the apex, but at least 3 cm from the cuff so that the suture line will not overlap with the mesh. In the occasional circumstances where posterior vaginal prolapse is the dominant vaginal prolapse, a posterior vaginal incision with a posterior approach to the sacrospinous ligament will be allowed.
3. Blunt or sharp dissection to approach the sacrospinous ligament extra-peritoneally.
4. After confirmation of the location of the ischial spine, the tapered lead and mesh assembly will be delivered into the sacrospinous ligament 1–2 fingerbreadths medial to the ischial spine.
5. The most cephalic edge of the mesh may be attached to the vaginal apex (post-hysterectomy) with sutures.
6. Mesh modifications are strongly discouraged; any exceptions will be documented on operative case report forms. Mesh orientation will be as described with body of mesh placed anterior (no flipping of mesh body to face posteriorly).
7. Tensioning to re-suspend the apex without tense mesh arms.
8. Ligation of enterocele is allowed as indicated with 0 or 2–0 delayed absorbable monofilament suture and may be attached to posterior aspect of mesh.
9. The distal most edge of the mesh (closest to the bladder neck) may be secured with sutures to prevent bunching or rolling of the mesh.
10. Vaginal closure with 2–0 polyglactin.

Sacral Colpopexy:

The technique for sacral colpopexy needs to be performed in similar fashion when performed by open, laparoscopic and robotic approach. Vesicovaginal and rectovaginal dissection will be performed in the usual fashion to allow placement of anterior and posterior vaginal mesh arms.

• Mesh:

- Standardize mesh characteristics: knitted, large pore (1800 mm), light weight (42g/m2), high porosity (60%) monofilament polypropylene mesh (no greater than GyneMesh™) will be allowed.
- Y-mesh or two separate arms will be allowed. The two arms may be attached using standardized suture per surgeon’s choice.

- No xenograft or allograft products
- No collagen coated mesh
- Mesh type and configuration will be tracked
- The length of the anterior, posterior and sacral arms implanted will be recorded.
- No minimum mesh length is required and is at surgeon's discretion.

- The mesh will be attached with a minimum of 4 attachment sites on each arm (anterior and posterior, 8 total). Additional attachment points are allowed as needed per surgeon's discretion. No self-locking sutures will be allowed.

- Suture: The protocol has standardized the suture type to minimize potential for suture exposure and erosion. Delayed or permanent monofilament absorbable suture will be used for attachment of mesh to the vagina.

- A minimum size of 2–0 suture is required (0 or 2–0). Given the reports of increase suture erosion, Gortex and braided permanent suture will not be allowed for vaginal attachment.

- Presacral dissection will be performed to allow for attachment of the sacral mesh arm inferior to the sacral promontory. A minimum of two permanent sutures or permanent anchors/tacks should be used to attach the mesh. The location will be tracked on intra-operative data form.

- Peritoneal closure is performed.

Table 5:**Additional Study Measures****Anatomic:**

- POP-Q points (Aa, Ap, Ba, Bp, C)
- Proportion of participants in each group with C > -2/3 TVL
- Maximum extent of prolapse (defined as leading edge of prolapse-Ba, C, Bp)

Functional:

- Prolapse: Patients Global Impression of Improvement (PGI-I)²⁷, Mean overall prolapse symptoms using POPDI-6 scores¹²
- Urinary: Duration of postop catheterization, Mean UDI-6 scores (sub-scale of PFDI-20)¹², De novo voiding dysfunction rates, De novo incontinence rates
- Sexual/Body Image: Mean PISQ-IR²⁸ and BIPOP scales²⁹, Rates of de novo dyspareunia
- Bowel - bowel function using CRADI-8 scores¹²
- Quality of Life Measures: General SF-12 scores and sub-scales³⁰, Pelvic QOL - mean PFIQ score¹², Katz ADL³¹, Functional Activity Scale³²

Regret/Satisfaction:

- Regret with Decision Regret Scale (DRS-PFD) and Satisfaction with Decision Scale (SDS-PFD)²³

Safety:

- Intraoperative safety: group comparisons of mean operative time, estimated blood loss, blood transfusion, intra- and postoperative complications categorized using a modification of the Dindo Classification³³
- Mesh-related complications: mesh exposure in the vagina or mesh erosion into another organ and the classification of the intervention:
 - None or non-surgical medical intervention only
 - Minor or intra-office surgical intervention
 - Surgery
- Rates of pain captured from the modified Surgical Pain Scale³⁴, pain medication use (during 24 hours prior to completing Body Part Pain Score), and location of pain with Body Part Pain Score.
- Pelvic infection: Perioperative infections, urinary tract infections, vaginal infections with flora uncommon to the vaginal canal
- De novo vaginal bleeding, atypical vaginal discharge, fistula formation, neuromuscular problems (including groin, buttock and leg pain).
- Need for subsequent procedures: any surgical or non-surgical treatment for pelvic floor disorders (including urinary incontinence, voiding dysfunction, defecatory dysfunction, fecal incontinence, recurrent prolapse, and dyspareunia/pelvic pain).
- Rates of vaginal scarring, defined as de novo scar requiring medical or surgical intervention.
- Rates of vaginal shortening (TVL<6cm), de novo dyspareunia, and worsening dyspareunia with AE survey.

Table 6:**Adverse Events Guidelines:**

-
- During the first six weeks following surgery: All AEs and SAEs of grade II or higher will be captured for the first six weeks following surgery.
 - During the 6-Month Visit: For the period between six weeks and six months capture all AEs and SAEs that are deaths, require a hospitalization or an emergency room visit, and all AEs of grade II or higher that are at least possibly related to the pelvis or surgery, in the opinion of the investigator.
 - At all remaining visits, only deaths and AEs and SAEs of grade II or higher that are at least possibly related to the pelvis or surgery, in the opinion of the investigator, will be collected.
-