CONFIDENTIAL

Pelvic Floor Disorders Network

Full-Protocol

Three-Arm Apical Suspension Trial for Post-Hysterectomy Vault Prolapse: Prospective Randomized Trial Involving Sacral Colpopexy, Transvaginal Mesh and Native Tissue Apical Repair
ID#: 27P01

Short Title: **A**pical **S**uspension Repair for Vault **P**rolapse **I**n a Three-Arm **R**andomize**d** Trial Design "ASPIRe"

Concept Approval: October 11, 2013
Mini Approval: January 17, 2014
Full-Protocol Approved: April 25, 2014
Version 1.0 November 24, 2015
Version 2.0 January 27, 2016
Version 3.0 December 5, 2016
Version 4.0 December 27, 2018
Version 5.0 April 18, 2019
Last Updated: February 12, 2021

Protocol Chair:

Shawn A. Menefee
3250 Fordham Street
Department of Ob/Gyn
San Diego, CA 92120
Phone: 619-221-6398
Email: shawn.a.menefee@kp.org

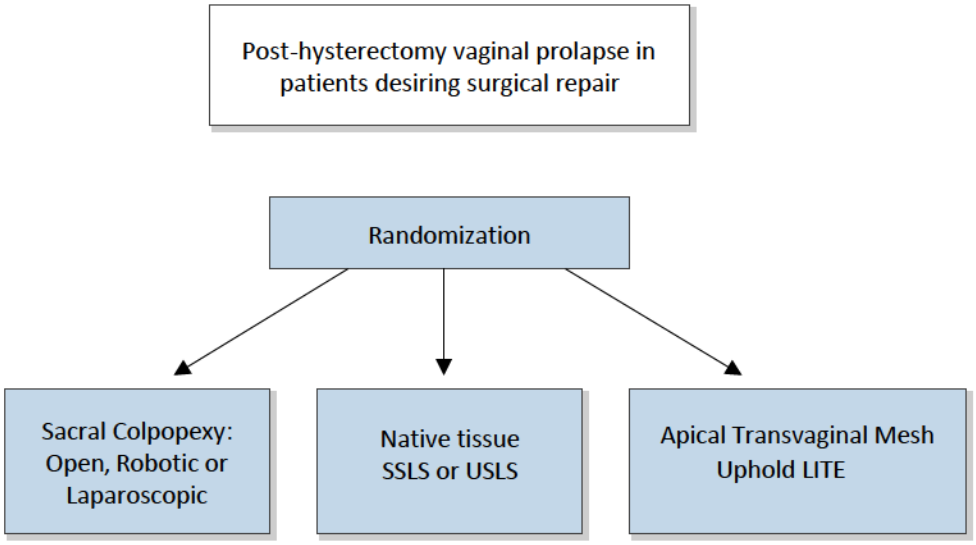
Protocol Working Group:

University of California at San Diego/Kaiser Permanente: Shawn A. Menefee, Chair
Duke University: Alison Weidner
University of Pennsylvania: Heidi Harvie
Cleveland Clinic: Marie Paraiso
Brown/Women and Infants Hospital of Rhode Island: Deb Myers
University of Alabama at Birmingham: Ed Varner
University of New Mexico: Gena Dunivan
University of Pittsburgh: Pamela Moalli
University of Texas Southwestern Medical Center: David Rahn
DCC RTI: Sonia Thomas
Eunice Kennedy Shriver National Institute of Child Health and Human Development: Donna Mazloomdoost

Version 6.0 (12Feb2021)

The information contained within this document is not to be disclosed in any way without the prior permission of the Protocol Chair(s), or the PFDN NICHD Program Scientist and Project Officer.

Flow Diagram of Protocol



*All groups may receive concomitant anterior and/or posterior repairs and full-length mid-urethral slings as indicated, per the discretion of the surgeon.

ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynecologists
AE	Adverse Event
AHRQ	Agency for Healthcare Research & Quality
AMS	American Medical Systems
ASA	American Society of Anesthesiologists
ASC	Abdominal Sacral Colpopexy
ASPIRe	Apical Suspension Repair for Vault Prolapse In a Three-Arm Randomized Trial Design
AUGS	American Urogynecologic Society
BIS	Body Image Scale
CARE	Colpopexy and Urinary Reduction Efforts
CEAC	Cost-Effectiveness Acceptability Curve
CRF	Case Report Form
DCC	Data Coordinating Center
CTCAE	Common Terminology Criteria for Adverse Events
DRS	Decision Regret Scale
DSMB	Data and Safety Monitoring Board
E-CARE	Extended Colpopexy and Urinary Reduction Efforts
FAS	Functional Activity Scale
Elevate-AA	Elevate Anterior & Apical Prolapse Repair System
FAS	Functional Activity Scale
FASt	Frailty ASPIRe Study
FDA	Food and Drug Administration
FPMRS	Female Pelvic Medicine & Reconstructive Surgery
GCO	Global Composite Outcome
HRQOL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IRB	Institutional Review Board
Katz ADL	Katz Index of Independence in Activities of Daily Living
LTC	Long-Term Care
MedDRA	Medical Dictionary for Regulatory Activities
MSM	Medical Safety Monitor
MITT	Modified Intent-to-Treat
NCI	National Cancer Institute
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NT	Native Tissue
NIH	National Institutes of Health
OPTIMAL	Operations and Pelvic Muscle Training in the Management of Apical Support Loss

OPUS	Outcomes Following Vaginal Prolapse Repair and Mid-Urethral Sling
OR	Operating Room
PASEo	Gaining the PAtient Perspective on Surgical Adverse Events
PFCS	Pelvic Floor Complications Scale
PFD	Pelvic Floor Disorders
PFDI	Pelvic Floor Distress Inventory
PFDN	Pelvic Floor Disorders Network
PISQ-IR	Pelvic Organ Prolapse Incontinence Sexual Questionnaire IUGA-Revised
POP	Pelvic Organ Prolapse
POPDI	Pelvic Organ Prolapse Distress Inventory
POPIQ	Pelvic Organ Prolapse Impact Questionnaire
POP-Q	Pelvic Organ Prolapse Quantification System
PPAR	Patient-Perspective in AE Reporting
PPT	Patient Preference Trial
PRO	Patient Reported Outcome
PVR	Post Void Residual
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SC	Sacral Colpopexy
SDS	Satisfaction with Decision Scale
SF-12SL	12-Item Short-Form Health Survey Support Loss
SNF	Skilled Nursing Facility
SSL	Sacrospinous Ligament
SSLS	Sacrospinous Ligament Suspension
SSQ	Surgical Satisfaction Questionnaire
SUPeR	Study of Uterine Prolapse Procedures - Randomized Trial
TOMUS	Trial of Mid-Urethral Slings
TVL	Total Vaginal Length
TVM	Transvaginal Mesh Repair
TVT	Tension-Free Vaginal Tape
TVT-O	Tension-Free Vaginal Tape-Obturator
UAB	University of Alabama at Birmingham
UCSD	University of California at San Diego
UDI	Urogenital Distress Inventory
UITN	Urinary Incontinence Treatment Network
UNM	University of New Mexico
USLS	Uterosacral Ligament Suspension
UTSW	University of Texas Southwestern Medical Center

TABLE OF CONTENTS

LIST OF TABLES

A. STUDY OBJECTIVE AND PURPOSE

The primary purpose of this three-arm randomized clinical trial is to determine if apical transvaginal mesh placement is non-inferior to sacral colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse and to determine if mesh reinforced repairs performed by abdominal or vaginal approach are superior to native tissue vaginal repair.

A.1. Primary Aims

A.1.a. Primary Aim 1

To determine if Apical Transvaginal Mesh is non-inferior to Sacral Colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years.

Primary Aim 1a

In the case where Apical Transvaginal Mesh is shown to be statistically significantly non-inferior to Sacral Colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years, to determine if Apical Transvaginal Mesh is superior to Sacral Colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years.

A.1.b. Primary Aim 2

To determine if Sacral Colpopexy is superior to Native Tissue Repair for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years.

A.1.c. Primary Aim 3

To determine if Apical Transvaginal Mesh is superior to Native Tissue Repair for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years.

Hypothesis

Treatment failure will not differ between vaginally and abdominally placed mesh for vaginal vault prolapse, and mesh repairs (regardless of route of implantation) will be superior to native tissue apical suspension.

A.2. Secondary Aims

A.2.a. Secondary Efficacy Outcomes

To compare detailed anatomic and comprehensive functional outcomes (including prolapse, urinary, sexual, bowel, and health related quality of life (HRQOL) across three methods of vault suspension.

A.2.b. Safety

To describe and compare safety, adverse events (including mesh erosion and exposure), pain, and need for subsequent procedures across three methods of vault suspension.

A.2.c. Predictors of Poor Outcomes

To identify risk factors for treatment failure, including method of vault suspension, baseline degree prolapse, age, obesity, smoking, menopausal status, estrogens, previous prolapse surgery, and predict higher treatment failure.

A.2.d Body Image

To describe changes in body image as measured by a validated scale (BIS) in a group of women undergoing apical repair with and without mesh and to evaluate whether or not changes in sexual function are associated with changes in body image.

A.2.e. Preference Evaluation

To assess patient and surgeon reasoning for declining participation in the trial. This will be determined by the CONSORT diagram for enrollment.

A.2.f. Cost Effectiveness

To compare the cost effectiveness of repair across the three methods of vault suspension.

A.2.g. Exploratory Aim (Global Composite Outcome)

To evaluate the development of a valid and reliable Global Composite Outcome (GCO) that balances adverse events and patient-centered outcomes to anatomic definitions of failure and success.

A.2.h. Patient-Perspective in AE Reporting (PPAR)

To evaluate the patient's perspective about adverse events and their role in patient decision-making outcomes. The aims of PPAR include comparing patient versus surgeon rankings of complication grade, outcome, expectedness and seriousness, to estimate the association between patient rankings of AEs with decision-making and quality of life outcomes, and to determine if their perspective about AEs changes over time. See Appendix B.

A.2.i. Frailty ASPIRe Study (FASt)

To determine the impact of preoperative frailty and mobility on surgical treatment outcomes and postoperative complications of older women following surgical correction of apical pelvic organ prolapse (POP). See Appendix C.

B. BACKGROUND AND SIGNIFICANCE

Pelvic organ prolapse (POP) is a common condition in women with more than 225,000 surgeries performed annually. [1] Loss of apical support is considered a key component when prolapse extends beyond the hymen. [2] At least half of the observed variation in anterior compartment support may be explained by apical support. [3] Because of the significant contribution of the apex to other levels of vaginal support, surgical correction of the anterior and posterior walls may be less successful unless the apex is adequately supported. [4]

Post-hysterectomy vaginal vault (apical) prolapse can be managed surgically with various techniques and approaches ranging from obliterative procedures to reconstructive procedures performed with the placement of grafts and mesh (apical transvaginal mesh repairs, sacral colpopexy) or with the patient's own tissue (native tissue repairs). Native tissue (NT)

apical vaginal repairs (uterosacral or sacrospinous suspensions) have demonstrated adequate reliability for subjective symptoms, but many reconstructive surgeons have concerns with long-term durability, adequate success rates with advanced prolapse, and development of prolapse involving anterior and posterior compartments.

While traditional native tissue vaginal repairs remain the most common approach to surgical correction of POP, there are some estimates that one out of three POP surgeries in 2010 used mesh with three out of four mesh procedures being completed transvaginally (industry source). [5] The impetus for this trend of increased vaginal mesh procedures was likely multifactorial, including: (1) increased industry marketing and training efforts, (2) common use of graft augmentation for other surgical procedures such as hernia repairs, (3) success of mid-urethral sling procedures, and (4) dissatisfaction with outcomes for native tissue POP repairs, with reoperation rates as high as 13% within 5 years and 30% over a lifetime for recurrent prolapse and/or urinary incontinence. [6-8]

The use of transvaginal mesh for POP repairs markedly increased until the FDA warning in 2011 described "serious complications associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence." [9] Despite evidence that transvaginal mesh (TVM) repairs are associated with improved anatomic success rates over native tissue repairs, concerns regarding rates of reoperation for mesh exposure (approximately 15%), vaginal pain, as well as lack of evidence that mesh resulted in better subjective outcomes, prompted calls for prospective evaluation of vaginal mesh procedures with long-term safety and efficacy assessments. [10, 11] Following the 2011 FDA communication, the FDA has issued orders to manufacturers in January 2012 to conduct postmarket observational studies to address specific safety and effectiveness concerns related to surgical mesh used for transvaginal repair of pelvic organ prolapse; and issued an order in January 2016 to reclassify the devices from class II, which are moderate-risk devices, to class III, which include high-risk devices. This classification requires that new products must undergo more rigorous testing prior to being approved by the FDA. Since the FDA announcement in 2011, vaginal mesh techniques have evolved to include the use of lighter weight mesh, decreased mesh load via the implantation of smaller pieces of mesh, trocar-free techniques, and alterations in surgical techniques to include deep dissection and transverse incisions. Published reports since the FDA announcement suggest that complication rates for vaginal mesh procedures on average are 5% (1.5%-17%) with less than 13% reoperation rates and more than 90% anatomic and comparable subjective success. [12]

While sacral colpopexy (SC) has long been considered the gold standard treatment of apical prolapse, it is the least commonly performed procedure and requires levels of skill beyond traditional or grafted vaginal surgery. There have been over 300 published reports on this approach and systematic reviews cite low erosion rates (< 5%), low dyspareunia rates (< 5%), and high success rates (90-95%). [13] However, SC procedures have longer operative times, higher associated costs, and require intraperitoneal access with the potential serious (albeit rare) adverse events of bowel injury, postoperative obstruction and sacral osteomyelitis. Sacral colpopexy procedures have been performed via open, laparoscopic and robotic approaches with comparable short-term success rates. [14-16] Although initially felt to have low mesh exposure, dyspareunia, and failure rates, long-term outcomes beyond 7 years for SC are less encouraging with reports of erosions up to 10% and POP failure of 24% to 48% depending on definition of failure. [17]

While many surgeons favor specific surgical approaches for vaginal vault prolapse, most surgeons choose the approach based on prior training and experience rather than scientific

evidence to guide their decision-making. In female pelvic medicine & reconstructive surgery (FPMRS) specialty practices, most women are offered all three approaches and the decision is made based on numerous factors. All apical surgical techniques have potential advantages and differing unique complications and there is an urgent need for randomized data comparing the newer available apical TVM procedures to SC and NT vaginal repairs.

B.1. Rationale for Operations Being Proposed for this Study

Current available treatment options for apical prolapse are outlined in the table below.

Table 1. Surgical Treatment Options for Apical Prolapse (Non-Obliterative Procedures Only)

	Post-hysterectomy Vaginal Vault Prolapse
Sacral Colpopexy	Robotic/Laparoscopic/Open
Native Tissue Options	Extraperitoneal Colpopexy: Sacrospinous Ligament Suspension (SSLS) Intraperitoneal Colpopexy: Uterosacral Ligament Suspension (USLS)
Vaginal Mesh Options	Extraperitoneal colpopexy with mesh (e.g. Uphold LITE) Extraperitoneal colpopexy with free hand mesh (Restorelle Smart Mesh)

B.1.a. Sacral Colpopexy

Sacral colpopexy has long been considered the gold standard for post-hysterectomy vaginal vault prolapse. The additional operative time and potential for serious complications, such as small bowel obstruction and osteomyelitis, must be balanced against the potential benefits of vaginal surgical techniques. Anatomic success rates range from 78% to 100%. [18] In contrast, the estimated long-term composite failure rate reported in the recent E-CARE trial was 48%. [17] The use of contemporary composite outcomes and higher than previously thought mesh erosion rates questions whether sacral colpopexy has the durability and long-term safety to be considered the gold standard operation for apical prolapse. Success rates for sacral colpopexy were well summarized by Barber. [19] (Appendix A: Table 7)

Sacral colpopexy approaches range from open to laparoscopic to robotic; however, it is commonly accepted that all approaches result in similar anatomic and subjective success rates with the main differences being operating time, hospital admission length, and postoperative pain scores and cost. [20] Even though performing the sacral colpopexy through a minimally invasive approach would allow for direct comparisons of hospital stay and postoperative pain levels to vaginal approaches, we feel the most important question to be answered is the ultimate surgical success outside of the immediate postoperative period. By allowing any approach to sacral colpopexy, this study allows the inclusion of all site surgeons and eliminates the learning curve for new procedures or referral to other surgeons. This approach is aimed at improving generalizability across various regions, allowing for local variation in surgical technique and approach.

B.1.b. Native Tissue Options

Native tissue repairs for post-hysterectomy vaginal prolapse remain a commonly used surgical technique. The OPTIMAL trial, a large randomized study that evaluated two commonly performed native tissue surgical repairs, found similar anatomic success rates of 60% using contemporary composite definitions in both treatment arms (SSLS and USLS) at 2 years. Given equivalent anatomic and subjective results found in that trial (even though majority of procedures were associated with hysterectomy), either SSLS or USLS will be allowed in this protocol. [21] We anticipate that majority of the NT repairs in post-hysterectomy apical prolapse will be performed by SSLS approach (> 75%).

The most commonly performed procedure in academic centers for uterine prolapse is an intraperitoneal colpopexy (USLS) (Appendix A: Table 8). While most prior studies are retrospective in nature using only objective definitions, uterosacral vault suspensions have a low overall recurrence rate of 4% to 18% with a reoperation rate of less than 7%. The most common native tissue repair for post-hysterectomy vaginal vault prolapse is an extraperitoneal colpopexy (SSLS) +/- anterior – posterior colporrhaphy (Appendix A: Table 9). While the majority of prior studies involving SSLS are retrospective in nature, SSLS failure rates range from 3% to 33%. Success rates for uterosacral operations and sacrospinous ligament suspensions were well summarized by Barber. [19]

B.1.c. Apical Transvaginal Vaginal Mesh Options

The FDA conducted a systematic review of the scientific literature on transvaginal mesh and in July 2011 published a report titled "Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse." [5] In this report they noted that in 2010 approximately 300,000 women underwent surgical procedures to repair POP; 1/3 used mesh, with 75% of mesh procedures performed transvaginally. Despite widespread use of TVM for apical support in clinical practice, there are limited data on the results of these procedures and systematic reviews on vaginal mesh for the apical compartment are inconclusive. Systematic reviews by the Society of Gynecologic Surgeons found weak evidence for improved anatomic success for anterior vaginal prolapse when repairs were performed with synthetic mesh compared with native tissue. [20] A systematic review of vaginal mesh kits for apical repair found that they appear effective in restoring apical prolapse in the short-term, but long-term outcomes are unknown. [22] Prospective studies with long-term validated outcome assessments are needed to understand the safety and efficacy of TVM for the apical compartment.

Although the use of transvaginal mesh has decreased since the 2011 FDA warning, approximately half (62%) of urogynecologists use transvaginal mesh in their practice. While 90% of respondents to an American Urogynecologic Society (AUGS) survey used synthetic mesh for POP repairs prior to the FDA warning, following the warning, 40% had decreased vaginal mesh use but only 12% stopped using vaginal mesh. [9]

A recent Cochrane review demonstrated improved anatomic success rates with TVM procedures compared to native tissue repairs. [13] However, the reoperation rates with TVM have been demonstrated to be highest among prolapse procedures. [23] The majority of the TVM techniques (kits) used in clinical trials are no longer available in the United States. Some surgeons have used traditional surgical techniques supplemented with mesh reinforcement. Such techniques would appear to offer an alternative to trocar-based TVM kits, but these modifications are not standardized. The secondary generation of TVM kits have some unique characteristics not found in the first generation trocar-based kits. These characteristics include a single smaller incision, unique apical attachment into the SSL, lack of trocar passage through skin and deep structures, and lighter weight and density compared to the first generation kits. Consequently, standardized and commercially available single incision non-trocar TVM procedures (which appears to offer clinical advantages over prior trocar-based mesh kits/techniques) will be used in this trial arm. Outcomes for single incision (non-trocar) TVM kits are reviewed in Appendix A: Table 10.

The concept of the TVM procedure evolved from the original trocar-placed device to trocar-less placement, with the most recent product developed by Boston Scientific (Uphold LITE™). This procedure is performed through an anterior approach using a synthetic

monofilament mesh bridge which attaches to the anterior or posterior vaginal wall and then bilaterally to the sacrospinous ligament. The most recent FDA approval on September 14, 2011 for the Uphold LITE Vaginal Support System indicated that "for tissue reinforcement and stabilization of fascial structures of the pelvic floor for vaginal wall prolapse, where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect". The Uphold LITE mesh has the same overall dimensions as the previous Uphold mesh, but has a 75% increase in pore size, a 38% reduction in weight, a 32% reduction in surface area ratio, and is blue for enhanced visibility if erosions occur. Recent investigations suggest that lighter, larger pore size mesh may have less stress shielding, which may ultimately result in lower rates of mesh erosion/exposure. [24, 25] Likewise, the American Medical Systems (AMS) Elevate Anterior and Apical Prolapse Repair System with IntePro Lite mesh was most recently approved by the FDA on June 20, 2012 with a modification to the apical needle passer sheath. The IntePro Lite is a type I macroporous polypropylene mesh that is 50% less dense and lighter than the first generation type I mesh (IntePro) used in Apogee/Perigee. The IntePro Lite mesh has similar pore size, weight, and surface area to the Uphold LITE mesh. Astoria, the manufacturer of Elevate kits, halted production of these kits in March 2016; thus, while the scientific data on outcomes and safety can be used for comparison for TVM, the Elevate kit will not be used in this trial. Theoretically, mesh exposure rates may also be lower with mesh strap techniques because of the smaller amount of mesh material used and the fact that the mesh straps are directed away from the vagina so that the mesh can be placed away from incision lines. Mesh strap techniques have limited published data among women with vaginal vault prolapse with most published reports being associated with hysteropexy.

A review of clinicaltrials.gov reveals that there are ongoing registered trials studying the Uphold procedure as a hysteropexy and vault prolapse:

1. VAULT study http://clinicaltrials.gov/ct2/show/NCT01377142?term=Vault&rank=1: "Vaginal Uphold Hysteropexy and Laparoscopic Sacral Hysteropexy for the Treatment of Uterovaginal Pelvic Organ Prolapse (VAULT)". This multi-center trial is sponsored by the Foundation for Female Health Awareness and coordinated at the Cleveland Clinic. This study is non-randomized and has 12-month outcome duration. Both groups retain their entire uteri and the primary outcome is a composite outcome (anatomic, subjective, and retreatment – similar to the outcome described in this ASPIRe protocol).
2. HUUT study http://www.anzctr.org.au/trial_view.aspx?ID=343047: "Hysterectomy or Uphold Uterine Conservation in women with apical prolapse – A Randomized Controlled Trial (HUUT)". This study was found in the Australian and New Zealand Clinical Trials Registry and is being performed in Victoria, Australia. This study is similar to the SUPeR protocol followed to 36 months.
3. Multi-center prospective non-randomized study of Uphold LITE versus native tissue for the treatment of women with anterior/apical pelvic organ prolapse: This study is sponsored by Boston Scientific to satisfy the FDA 522 requirement and is currently enrolling.
4. Prospective non-randomized single cohort with 214 participants including uterine and cuff prolapse with Uphold LITE: This study's primary author is Altman and has a primary outcome of safety and complications with secondary outcomes of objective and participant measures. The study has completed enrollment.
5. Multi-center prospective randomized clinical trial (SUPeR) to compare the effectiveness and safety of two transvaginal apical suspension strategies for uterovaginal prolapse: a

mesh augmented hysteropexy versus vaginal hysterectomy and uterosacral ligament suspension (USLS): The study has completed enrollment.

Published Studies on Uphold LITE TVM Kit:

1. A prospective multi-center non-randomized single cohort of Uphold LITE mesh for the surgical treatment of uterine-predominant prolapse with 120 subjects is published in French with safety and anatomic measures (this trial was primarily hysteropexy).
2. A single site longitudinal case series published in French reported on 59 patients undergoing an Uphold procedure for uterovaginal prolapse revealed an anatomic success rate of 93% at mean follow-up of 12 months with a mesh exposure rate of 3.5%. [26]
3. Vu and Goldberg et al. reported on the first 115 Uphold subjects. Defining failure as C > 0, and Aa > 0, they found short-term failure rates of 0%-4.2%, depending on the group, with total 2.6% mesh exposure rates. Anatomic failure rates, mesh erosion rates, dyspareunia rates, and patient satisfaction rates are very encouraging. [27] They reported on 47 women undergoing repair for vault prolapse using Uphold who had recurrence rates ranging from 0% in those with prior hysterectomy to 4.2% in those undergoing concurrent hysterectomy. The rate of mesh exposure was 3/115 (2.6%), including two in women with concurrent hysterectomy. Self-reported dyspareunia was more common preoperatively (13.4%) than postoperatively (9.3%). PFDI scores improved in all domains, and 93% of those who completed the Surgical Satisfaction Questionnaire (SSQ) reported they were satisfied and would choose the surgery again. [27]
4. Jirschele K et al. reported on 99 patients who underwent bilateral sacrospinous hysteropexy with polypropylene mesh in a multi-center, prospective trial followed to 12 months. The composite outcome revealed success of 97%. The overall mesh erosion rate was 6.52% and the overall reoperation rate was 7%. [28]
5. Letouzey et al. reported on 115 subjects with a minimum of 12-month follow-up and mean follow-up of 23 months. Of note, only 13 subjects (11%) had prior hysterectomy and 19 subjects (17%) had concomitant hysterectomy leaving the remaining 83 subjects undergoing mesh hysteropexy. The anatomical success rate was 93% with a patient satisfaction rate of 95%. The reoperation rate for mesh complications was 3.4%. [29]

A review of clinicaltrials.gov reveals that there are ongoing registered trials studying the Elevate procedure in hysteropexy and vault prolapse:

1. The Sacrocolpopexy versus vaginal mesh procedure for pelvic prolapse is a randomized controlled trial with 60 participants. This study is ongoing but not recruiting patients.
2. A prospective safety and efficacy cohort study of Elevate-AA prolapse repair system compared to native tissue repair for pelvic organ prolapse repair. The estimated enrollment is 494 and part of the FDA 522 study requirements.

Published Studies on Anterior/Apical Elevate:

Similar to previous published Uphold LITE studies, the Elevate-AA literature has various operative characteristics involving hysteropexy, concomitant hysterectomy, and vault prolapse. In addition, publications also include reports on Posterior Elevate and several publications with

both Elevate-AA and Posterior Elevate placed concurrently. Thus, we will outline the reports of Elevate-AA only in this section (see Appendix A: Table 10 for review of single incision slings).

1. The first report of Anterior/Apical Elevate by Moore et al. in 2012 involved 60 subjects from a retrospective review with average follow-up of 13.4 months (3-24 months), including 44% with prior hysterectomy. The anatomic success rate was 92% and no mesh exposure. [30]

2. Stanford et al. initially reported on a prospective series of 142 participants in 2012, which has been updated with extended follow-up (24 months) in 2015. In this trial, 61 subjects had prior hysterectomy and 19 subjects (17%) had concomitant hysterectomy leaving the remaining 83 subjects undergoing mesh hysteropexy. In the total group, the apical success rate was 96.2% and the anterior success rate was 82%. In the post-hysterectomy group (n = 61), the apical success rate was 93.5% and the anterior success rate was 80%. Of note, the missing data was high in the apical arm at 24 months. Mesh extrusion was 4.9% in the post-hysterectomy group. [31, 32]
3. Rapp et al. reported on 40 subjects available for 24-month follow-up in this retrospective review. There were 21 subjects with prior hysterectomy. This study reported total success rates and did not sub-divide by operative characteristic. The anatomic and subjective success rates were both 90%. The mesh exposure rate was 5%. [33]
4. Lo et al. performed a prospective case series of 65 patients with stage III and IV POP followed for 12 months. The objective success rate was 97% and the subjective success rate was 94%. There were no mesh exposures. [34]
5. Marschke et al. performed a retrospective review of 70 post-hysterectomy patients who received the Elevate-AA procedure with mean follow-up of 13 months. Overall anatomic success rate was defined as leading edge less than or equal to stage 1. The anatomic success rate was 96% and the mesh erosion rate was 5.7%. [35]

Data are limited on apical TVM techniques and therefore they need to be studied. Furthermore, much of the literature for mesh apical suspensions does not provide breakdowns of the procedures. Over 38,000 Uphold kits, including all prior generations (Uphold and Uphold LITE), have been sold worldwide since its launch in 2008. Likewise, total Uphold kits sold in the U.S. since its launch is approximately 34,000 with 3,944 worldwide and 2,211 in the U.S. in the past 12 months (personal communication 9/2015) but their usage for uterine prolapse versus vault prolapse indications is not known. Likewise, there have been 57,000 Elevate Anterior & Apical Prolapse Repair System (Anterior/Apical Elevate) since product launch to the end of 2014 (personal communication 9/2015). In the United States, there were several apical TVM options marketed (one trocar-based kit, one free hand mesh, and three non-trocar kits) at the time of protocol development. The published reports on these non-trocar single incision apical TVM kits (while primarily are retrospective or non-randomized prospective studies and involve a wide range of surgical setting involving concomitant hysterectomy, hysteropexy, and post-hysterectomy vault prolapse) reveal similar success rates and high safety profiles. In December 2011, AUGS and American Congress of Obstetricians and Gynecologists (ACOG) published a joint committee opinion on “Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse” in which one of their recommendations was: “Rigorous comparative effectiveness randomized trials of synthetic mesh and native tissue repair and long-term follow-up are ideal.” Vaginal mesh is probably the most controversial topic in our field and it can be argued that the Pelvic Floor Disorders Network (PFDN) is the best group to study it. Our network can successfully perform unbiased and rigorous long-term comparative safety and efficacy studies that are

needed to comprehensively assess the role of mesh in prolapse surgery compared to other apical prolapse procedures.

In this study we are proposing a non-trocar single incision apical TVM kit as the approach for several theoretical reasons:

1. Trocar-based methods are no longer available in the United States.
2. Additional mesh placed in the ischiorectal fossa with trocar-based suspensions do not contribute to the repair and increases mesh burden without clear benefit.
3. Direct and accurate attachment to the SSL.
4. Surgeons in this network are comfortable with direct SSL techniques (OPTIMAL and SUPeR trial experience).
5. Lastly, free hand vaginal mesh is infrequently performed and difficult to learn and standardize, making non-trocar-based kits the only viable option.

After careful consideration of all single incision apical TVM options, we have elected to use Uphold LITE for the following reasons:

1. **Mesh Load:** The low-density mesh in Uphold LITE is similar to the proposed characteristic for the SC mesh used in this study. While the mesh load may be less for TVM kits compared to SC, traditional NT repairs can be performed for anterior, posterior, and ligation of the enterocele at the discretion of the surgeon if mesh coverage is deemed inadequate.
2. **Experience** with the index surgery: While Uphold Hysteropexy is a different procedure from Uphold LITE for post-hysterectomy apical prolapse, our network has experience in Uphold LITE as a TVM repair. This eliminates a potential limitation of the study results (that site surgeons were still in their learning curve for the TVM arm).
3. The **vaginal incision is not directly over the mesh** in Uphold LITE technique. While there is no clear evidence that this impacts future mesh exposure, it is logical that if an incision dehiscence occurs with underlying mesh an exposure is more likely.
4. Vaginal incisions are smaller and there is less dissection with Uphold LITE.
5. The free hand mesh option (Restorelle DirectFix and Restorelle L), while approved for vaginal insertion, lacks the standardization of Uphold LITE. We believe this lack of standardized technique would require additional learning and proctoring not available at the clinical sites. In addition, the available literature (even in the form of retrospective and prospective cohorts) makes it difficult to justify as a viable option for the apical TVM arm.

B.2. Prior Randomized Controlled Trials for Apical Prolapse

B.2.a. Sacral Colpopexy versus Sacrospinous Ligament Suspension

Three randomized trials have been published comparing SC to SSLS. The Cochrane review on the surgical management of POP concluded that SC was superior to SSLS for prolapse $\geq$ Stage 2, recurrent vault prolapse, postoperative stress urinary incontinence, and less postoperative dyspareunia. However, there were no statistically significant differences in objective failure from any site, subjective failure, reoperation for POP, or patient satisfaction, and SC took longer to perform and was more expensive. [13] The success rates for SC vs.

SSLS were well summarized by Barber in Table 2. [19] In the three randomized controlled trials (RCTs) involving relatively small number of subjects, the objective success rates ranged from 58% to 91% for ASC and 29% to 80% for SSLS.

Table 2. RCTs Comparing Abdominal Sacrocolpopexy (ASC) versus Sacrospinous Ligament Suspension (SSLS)

	n	Mean F/U mos)	Outcomes ASC v SSLS	Major complications	Reoperation rate ASC v SSLS
Benson 1996	80*	29 mos (12-78 mos)	Optimal [a] 22/38 (58%) v 12/42 (29%)	Dyspareunia 0/15 v 15/26 (58%)	6/38 (16%) v 14/42 (33%)
Lo 1998	118**	25 mos (12-74 mos)	49/52 (94%) v 53/66 (80%)	Dyspareunia 1/52 (9%) v 7/66 (39%)	Not stated
Maher 2004	95	24 (6-60 mos)	Subjective [b] 43/46 (94%) v 39/43 (91%) Objective [c] 35/46 (76%) v 29/42 (69%)	Dyspareunia 1/52 (9%) v 7/66 (58%), UI 23% v 44%	6/47 (13%) v 7/43 (16%)

*Recruitment halted after first interim analysis showed superiority of abdominal route.
**138 randomized, but 20 excluded after randomization for inability to follow-up.
a. Optimal cure defined as no prolapse symptoms, no anatomic defect beyond the hymeneal ring
b. Subjective cure defined as no symptoms of POP
c. Subjective cure defined as no symptoms of POP, anatomic defect less than Baden-Walker grade 2 (prolapse to the hymeneal ring)

B.2.b. RCTs of Vaginal Mesh

Several RCTs have been performed with vaginal mesh compared to native tissue repairs demonstrating superior anatomic success rates with similar subjective success rates. [11, 37, 38] However, these trials have been performed primarily for anterior vaginal POP. One study compared laparoscopic sacral colpopexy to total vaginal mesh for vaginal vault prolapse. This study demonstrated that at 2 years the laparoscopic sacral colpopexy had a higher satisfaction rate and objective success rate than the total vaginal mesh, with lower perioperative morbidity and reoperation rates. This has limited value since the vaginal mesh repair kit (Prolift) is no longer available in the United States. [39] There are currently no RCTs comparing currently available apical vaginal mesh kits to each other or to either native tissue apical repairs or sacral colpopexy.

In conclusion, the purpose of this study is to compare abdominal sacral colpopexy to transvaginal mesh and sacral colpopexy and transvaginal mesh repair to vaginal native tissue repairs for apical prolapse. At this point in time, there is no strong evidence that either uterosacral or sacrospinous ligament suspension is superior as a vaginal native tissue repair; thus, investigators may use their preference for either of these native tissue suspensions. For the apical TVM arm of the study, a specific non-trocar mesh procedure will be studied, namely the Uphold LITE procedure which will be performed according to manufacturer recommendations. For abdominal sacral colpopexy, all current techniques including open, laparoscopic, and robotic have similar objective success and any approach will be allowed for SC arm. [14-16] The sacral colpopexy will be performed in a similar fashion by all approaches.

B.3. Rationale for the Exclusion Criteria

The rationale for the exclusion criteria primarily involves elimination of potential subjects with history of use of materials or procedures that are to be involved in the index study. This history includes prior use of synthetic mesh and prior known SSLS performed for correction of either uterovaginal or post-hysterectomy apical prolapse. The usual clinical practice for post-hysterectomy apical prolapse is mixed with proponents on both sides of the spectrum having their biases with limited clinical data to support their surgical choices. While many surgeons routinely perform NT repairs as their primary surgery for patients with prior formal apical suspension at time of hysterectomy, a similarly large group only use mesh-augmented repairs.

After polling the PFDN sites, the group determined that exclusion of KNOWN prior SSLS at the time of hysterectomy or post-hysterectomy apical repair would have minimal impact on eligible candidates and make the exclusion criteria cleaner. Given that some form of uterosacral attachment (McCall Culdoplasty, attachment of uterosacral ligaments to vaginal cuff, and USLS) is commonly performed in association with hysterectomy for both POP and non-POP indications and there have been concerns that many of these procedures are often classified as formal USLS, we have elected to allow prior USLS at time of hysterectomy and for post-hysterectomy vaginal vault repair. Likewise, it is common in clinical practice to perform SSLS after prior USLS as a Native Tissue option. Those patients with known prior formal USLS randomized into the Native Tissue arm will have a SSLS performed. For those with unknown indications and/or procedures for POP at the time of hysterectomy, we will allow randomization unless evidence of prior mesh or graft is evident on clinical examination or prior known SSLS. Given that many patients present years after their hysterectomy and are unclear about prior “suspension” surgeries performed at the time of hysterectomy, we did not believe that this will impact surgeon’s decision making.

NT repairs are one of a number of appropriate choices of surgical intervention in that situation. The working group also considered whether or not women with prior use of biologic grafts should be excluded. Even though many biologic materials are believed to remodel to resemble host tissues, some materials (such as cross-linked xenografts) are potentially permanent. Given the unknown long-term effects of biologic materials, we have elected to exclude all women with KNOWN history of biologic materials used for reconstructive prolapse repairs in the anterior, apical, and/or posterior compartments. Although the use of biologic materials appears to have minimal impact on the ability to perform repeat surgeries, especially when performed for anterior and posterior vaginal reconstruction, the ability to determine location and prior attachment points is often lacking. The use of synthetic materials implanted for anti-incontinence procedures will not be excluded since their impact on the index reconstructive procedure are thought to be minimal. Patients with an unknown adverse reaction (such as erosion, pain, infection) to synthetic material will be excluded. Because reconstructive surgery with and without the use synthetic mesh has been associated with potential for vaginal pain, we have elected to exclude patients with unresolved chronic pelvic pain. Likewise, prior abdominal and pelvic radiation can impact wound healing and result in co-morbidities associated with the index surgery and thus is an exclusion. Relative contraindications to abdominal and vaginal surgeries are rare and surgeons differ in their clinical and surgical expertise and experience of patients’ factors that precluded them for performing certain surgical approaches. The group did not want to be too broad in exclusion criteria, thus limiting feasibility and generalizability, but have agreed the following conditions make either vaginal or abdominal difficult and may potentially impact patient safety or outcomes.

The following have been added as exclusion criteria to the ASPIRe protocol:

- Prior abdominal and/or pelvic radiation
- Known Horseshoe Kidney or Pelvic Mass overlying the sacrum
- Active diverticular abscess or active diverticulitis
- Shortened vaginal length (< 6 cm TVL)

B.4. Rationale for the Inclusion Criteria

The study will include adult women 21 years of age or older with prior hysterectomy. This eliminates the potential difficulties of treating women with a history of prior supra-cervical hysterectomy. These difficulties include the potential need to remove the cervix in some procedures, such as NT repairs, and the advantage of leaving the cervix in others (SC and TVM procedures). The need to perform a trachelectomy in some groups and not others makes study design and outcomes more confusing for a relatively small number of subjects. In addition, we believe that the number of otherwise eligible potential subjects with prior supra-cervical hysterectomies will be low.

Recent studies have demonstrated that prolapse beyond the hymen highly correlates with subjective symptoms of prolapse. [40, 41] Likewise, recent PFDN studies have used any prolapse at or above the hymen as an outcome measure of success. Because this study involves women with post-hysterectomy vaginal cuff or apical descent, vaginal cuff descent must be included as an inclusion criterion. The vaginal cuff must descend into at least the lower two-thirds of the vagina. While descent of point C into the lower half of the vagina has been used in recent PFDN apical trials (OPTIMAL/SUPeR), these studies included subjects with a cervix, which potentially serves as a confounder to actual apical support. In patients with a cervix, point C can often descend 1/3 of the TVL in asymptomatic patients with normal support. Because ASPIRe is a study of post-hysterectomy apical prolapse, we believe that descent of point C into the lower two-thirds of the vagina with leading edge of prolapse beyond the hymen is the optimal criterion for anatomic inclusion. Good clinical practice dictates that the presence of prolapse or bulge symptoms must be present in order to offer surgical management of POP. The use of Question 3 of the PFDI-20 has been used in prior PFDN studies and is from a validated questionnaire. The potential subjects must desire surgical correction of their prolapse and be available for 60-month follow-up. We have used 60-month follow-up to meet follow-up guidelines set forth by the FDA in their 522 recommendations allowing the last patient to have a minimum of 36-months of follow-up.

B.5. Rationale for Primary Outcome

The definition of success in prolapse surgical trials has been variable even within the PFDN. However, the use of composite outcomes is now standard both outside and within this network. In previous PFDN trials, we have used three main components including: 1) retreatment for prolapse with either pessary or surgery; 2) subjective symptoms of bothersome vaginal bulge symptoms as assessed by the prolapse question (“Do you usually have a bulge or something falling out that you can see or feel in your vaginal area”- Question 3 of the PFDI-20. This should be a positive response and bother related to this question); and 3) objective measurements using POP-Q.

While the definition of retreatment for prolapse has not changed from previous trials, the subjective and objective measures to assess prolapse success have been refined over the last five trials involving apical prolapse (CARE, OPUS, E-CARE, OPTIMAL, and SUPeR). This evolution has included careful analysis of outcome measures involving these studies. [42, 43]

The argument for this evolution was previously outlined in the SUPeR protocol. Even though SUPeR required omission of point C since the two groups differ postoperatively from each other in that one group retains a uterus, the main points remain significant even in a post-hysterectomy surgical trial. In order maintain consistency with current trials and to base study design on our network's recommendations, we propose using the same primary outcome measures as the SUPeR trial. The detailed rationale for the primary outcomes is discussed in the following paragraphs, as outlined in SUPeR protocol.

Over the last several years there has been increasing clarity defining success in prolapse surgery. The PFDN has led this effort with some important publications including "Defining Success After Surgery for Pelvic Organ Prolapse". [42] In this study using CARE data, the participant's assessment of overall improvement and rating of treatment success were compared between surgical success and failure for each of 18 surgical success definitions used. The results of this study, along with the emerging data on the distribution of pelvic support loss in the general population, led the authors to conclude that success should be defined as:

1. Absence of bothersome bulge symptoms
2. Absence of retreatment
3. Use of the hymen as a threshold for anatomic success

Further support for emphasizing the most distal measure of prolapse as the most important prolapse outcome measure comes from another PFDN study "Quantification of vaginal support: are continuous summary scores better than POP-Q stage". [43] In this study pooled baseline data from 322 CARE patients, 380 OPUS patients and 439 ATLAS patients was used to evaluate and compare 3 continuous summary support loss (SL) variables (which contained C point measures), POP-Q ordinal stages, and SLmax (location of the single most distal point). SLmax demonstrated the greatest responsiveness and the best correlation with POPDI, POPIQ, PFDI Question 4, and PFDI Question 5 (NOTE: The PFDI Question 5 is PFDI-20 Question 3 and the PFDI-20 will be used for this study). The authors recommended that "given its ability to provide an easily understood measure of maximum vaginal descent and its high responsiveness, SLmax may serve as a good primary outcome in studies evaluating prolapse treatment". They further stated that "if the aim of a surgical procedure is to restore support to a specific compartment, it is logical to provide descriptive statistics for the preoperative and postoperative status of that compartment."

For this study, we considered including a measure of apical descent "point C" in the primary outcome, but there are several problems with this inclusion including:

1. Most evidence supports that it is the most distal point that produces symptoms. If there is significant loss of support C, there is usually prolapse of the anterior (or posterior) wall more distal to that and therefore measurable in our outcome.
2. There are no evidence-based data at which point does "point C" become symptomatic when it is above the hymen.

For these reasons, we think it is important not to base the primary outcome on a C measure at or above the hymen. The degree of descent of point C above the hymen was used as a definition of failure in prior PFDN studies. In the OPTIMAL and CARE studies, the definition was the following: "If POP-Q point C descends more than one-third of TVL (C > -2/3*TVL; i.e. when TVL = 9, -5 is a failure by this criterion but -6 is not a failure)". However, point C will be

considered a failure if this point descends past the hymen. Treatment success is the primary outcome and treatment success is defined as:

1. Absence of bothersome bulge symptoms
2. Absence of retreatment
3. No prolapse past the hymen (points Ba, C, and Bp $\leq$ 0 cm)

Change in point C measures at or above the hymen; however, will be an important secondary outcome with a specific analysis plan and included in the primary publication.

B.6. Rationale for Using Both Non-Inferiority and Superiority Hypothesis

In the process of designing a clinical trial for post-hysterectomy vaginal vault prolapse, the Steering Committee and working group wanted to include the most common reconstructive procedures performed in clinical practice. Given this goal, the discussion revolved around the common clinical perceptions, scientific goals, and feasibility of a three-arm study involving the three major classifications of reconstructive surgeries for vaginal vault prolapse (Vaginal NT Repairs, Sacral Colpopexies, and Apical TVM).

Discussions with the protocol working group on alternative study designs reached a consensus that sacral colpopexy is considered the gold standard procedure for vaginal cuff prolapse. The group considered using a hypothesis test based on superiority to compare transvaginal mesh to sacral colpopexy; however, given the assumption of the anatomic success rates of 80% in both mesh arms (i.e. there is no evidence of a difference in success rate of the two arms), a sample size of 650 for these two arms would be required to test a two-sided hypothesis test of superiority in either direction that could detect a minimally important clinical difference between the arms. This sample size was not felt to be feasible for our network. The use of a design in clinical trials that tests the non-inferiority of one treatment regime to an alternative is typically performed in the setting of comparison of a standard treatment to a novel treatment that has fewer adverse effects, lower cost, and easier application, or in the case of medications, fewer drug interactions. Given that apical transvaginal mesh procedures are newer procedures with limited randomized trials, offer several potential advantages over sacral colpopexies of being less invasive with shorter operative times, and do not require entry into the abdominal cavity, a non-inferiority hypothesis is an appropriate method for comparing these treatments.

In the development of primary aim 1, which is to determine if apical TVM (Uphold LITE) is non-inferior to Sacral Colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 to 5 years, the use of the non-inferiority hypothesis was determined to be appropriate. Given the currently available clinical data using composite outcome measures, the working group assumed an 80% success rate in both mesh arms. In addition, the use of one-sided testing was determined to be appropriate given the design to test if apical TVM is non-inferior to SC. The working group determined that a 15% difference in anatomic success rate would be clinically relevant given the less invasive nature of apical TVM procedure. The use of one-sided testing of the non-inferiority arm provides a feasible sample size and would allow us to determine the following in the primary analysis:

- If TVM is non-inferior or inferior to SC in anatomic correction.
- If we will still be able to demonstrate if TVM is superior to ASC.

- If we will not be able to demonstrate that SC is non-inferior or inferior to TVM (most believe this will not be the case).

The working group consensus was that the main clinical question for primary aim 1 is to compare TVM to the "gold standard" SC and the determination that TVM is non-inferior to SC is the most clinically relevant question. Thus, one-sided testing would be appropriate to decrease sample size and improve study feasibility.

The superiority hypothesis for the native tissue arms is based on the common assumption that mesh reinforced repairs have better anatomic outcomes than native tissue repairs; were this not the case, native tissue repairs would likely currently be used exclusively for apical prolapse repair. This assumption is based on limited outcome data outlined in the recent Cochrane review. [14] Based on this assumption, the working group recommends a superiority design for comparing native tissue arms to both types of mesh-reinforced repairs (TVM and SC) (see primary aims 2 and 3).

Given the complexity of a three-arm trial and common clinical assumptions, the working group has elected to design this study using non-inferiority and superiority hypothesis as most valid and feasible for constructing comparisons among the three treatment arms.

B.7. Significance and Innovation

Only three RCTs have been performed for apical prolapse comparing sacral colpopexy to sacrospinous ligament suspension. While these studies demonstrate increased anatomic success of sacral colpopexy over native tissue repairs, they lack large numbers and contemporary definitions of success. Likewise, only one RCT has been performed comparing sacral colpopexy to TVM. While this study demonstrated higher satisfaction rates and objective success with sacral colpopexy, the vaginal mesh kit used in this study is no longer available in the United States. The recent FDA warning on vaginal mesh has resulted in a significant change in the use of vaginal mesh with limited vaginal mesh options available in the United States. However, an AUGS survey and industry internal numbers reveal the continued use of vaginal mesh in clinical practice. Recent statements from the FDA, ACOG, and AUGS have stressed the need for well-performed randomized clinical outcome studies comparing vaginal mesh to established surgical alternatives (FDA, ACOG Committee Opinion, and AUGS position statement). The PFDN is one of the few organizations capable of performing a three-arm randomized clinical trial comparing traditional surgical procedures to currently available vaginal mesh kits.

This study will be the largest post-hysterectomy vaginal vault prolapse trial ever performed and the only trial to assess the three surgical techniques used in clinical practice. Likewise, the study will include TVM, which has been commonly used in clinical practice but lacks well performed clinical trials.

B.8. Feasibility

While a three-arm study for post-hysterectomy vaginal vault prolapse is preferred to assess the three major categories of repairs, this increases the sample size of the trial compared to two-arm trials. The current PFDN sites vary in the performance of these differing categories of repairs in their usual practice; however, the number of procedures performed for post-hysterectomy vault prolapse remains high with numbers approaching 950 (943) annually. Considering a two-year enrollment period involving 363 randomized and treated subjects, this would represent 23 subjects per site annually or approximately 2 subjects per month. To reach

this goal with current PFDN sites, the enrollment would need to involve randomization of 19% of surgical patients undergoing repair for post-hysterectomy vaginal vault prolapse based on all clinical sites' surgical volume.

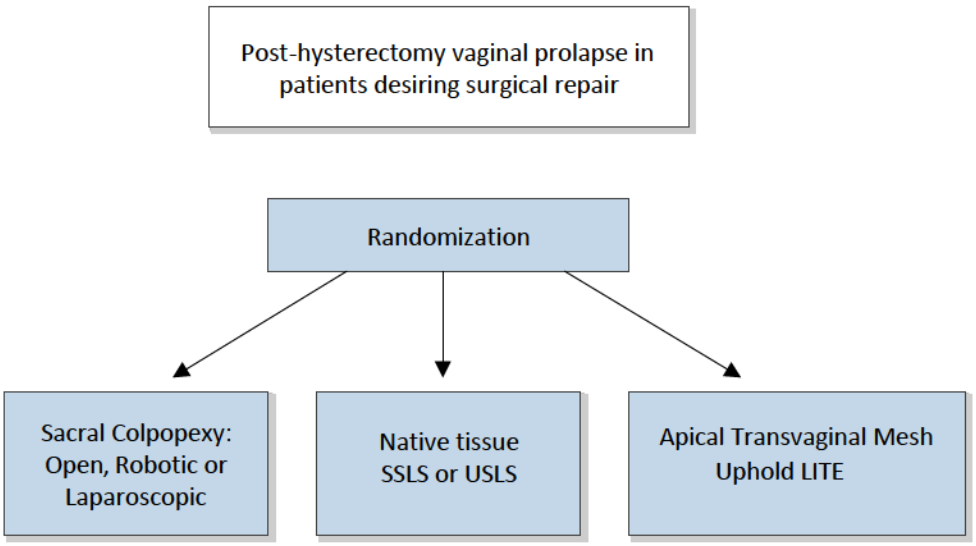
Annual PFDN Surgical Volume involving Post-Hysterectomy Vaginal Vault Prolapse:

SITE	Number
Brown	80
Cleveland Clinic	206
Duke	100
Penn	50
Pitt	159
UAB	164
UCSD	124
UNM	60
UTSW	80

C. STUDY SCHEMA

A figure illustrating the study design is depicted below.

C.1. Study Design Diagram



*All groups may receive concomitant anterior and/or posterior repairs and/or full length mid-urethral sling as needed, per the discretion of the surgeon.

C.2. Study Design

The study is a multi-center, randomized surgical trial of women with symptomatic post-hysterectomy apical (cuff) prolapse desiring surgical treatment. This study will compare the three available surgical treatments performed in usual practice. The purpose of this study is to compare two commonly performed mesh apical repair (Sacral Colpopexy vs. Apical Transvaginal Mesh) and vaginal native tissue apical repairs with mesh reinforced repairs. The primary outcome is measured over time (up to 60 months) using a survival analysis approach.

C.2.a. Superiority versus Non-Inferiority

Discussions with the protocol working group on alternative study designs reached a consensus that sacral colpopexy is largely considered the gold standard procedure for apical prolapse and given that vaginal mesh repairs offer several potential advantages, including less operative time and prevention of entry into the abdominal cavity, that a non-inferiority design would be most appropriate in the comparison of TVM to SC. Because testing superiority after showing non-inferiority is a closed testing procedure, we will also test superiority of TVM to SC if TVM is shown to be non-inferior to SC. When comparing mesh reinforced repairs to native tissue repairs, while the advantages of not using mesh is present, prior studies suggest increased efficacy in mesh groups; thus, a superiority design will be used to compare native tissue to the mesh groups (see Section B.6.).

C.2.b. RCT vs. PPT vs. Cohort

A Patient Preference Trial (PPT) is typically considered when the RCT group is not generalizable to the population at large. A RCT involving SC and TVM with a native tissue cohort was considered, but concerns over differing patient characteristics in the native tissue cohort made consensus difficult. Therefore, we believe the RCT is far preferable to a PPT and cohort trial and makes the study design more scientifically valid.

D. STUDY POPULATION

The study population will be adult women ($\geq$ 21 years of age) with symptomatic vaginal prolapse beyond the hymen who desire surgical management. A subset of these women who are $\geq$ 65 years of age will undergo additional assessments to measure preoperative frailty and mobility. This protocol will adhere to the CONSORT guidelines for performing and reporting randomized controlled trials. Women who are eligible but decline enrollment will be characterized in a manner consistent with the CONSORT requirements.

E. INCLUSION AND EXCLUSION CRITERIA

E.1. Inclusion Criteria

1. Women 21 years of age 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

E.2. Exclusion Criteria

1. Previous synthetic material or biologic grafts (placed vaginally or abdominally) to augment POP 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 chronic pelvic pain-active
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 active diverticulitis
    c. Shortened vaginal length (< 6 cm TVL)

*NOTE:

- Only documented SSLS will be an exclusion.
- Mesh used for only mid-urethral sling will NOT be an exclusion.
- If prior POP repair is unknown and unable to be documented, subjects will be eligible based on clinician judgment. The investigator will examine and assess for evidence of mesh or graft; if no evidence of mesh or graft is present on examination, subject remains eligible.

F. PARTICIPANT SCREENING

It is anticipated that subjects will come from the practices of PFDN investigators. Subjects with bothersome prolapse complaints and prolapse beyond the hymen will be offered the range of therapeutic options consistent with the physician's practice including, but not limited to, expectant management, conservative treatment, and abdominal or vaginal surgery for their condition. Those subjects desiring surgery will be offered participation in this trial. The pelvic organ prolapse quantitative exam and a bothersome bulge question (Question 3 of the PFDI-20) are used routinely in clinical care and will be used to determine eligibility.

Objective: Pelvic Organ Prolapse Quantification (POP-Q)

The pelvic organ prolapse evaluation will be performed according to the guidelines established by the International Continence Society. [44] The procedure will be standardized as demonstrated in a DVD produced by Duke University Medical Center ("Pelvic Organ Prolapse Quantification Examination"). Examinations will be performed in the dorsal lithotomy position with the participant straining maximally. Participants will be asked to confirm that the extent of prolapse demonstrated during the examination is consistent with the maximum degree of prolapse seen in their daily life. Standing POP-Q examinations will be performed if maximal prolapse cannot be demonstrated in the dorsal lithotomy position.

Subjective: Participants will be considered as having bothersome vaginal bulge symptoms if they report a positive response to PFDI-20 Question 3 and any degree of bother (i.e. any response other than "not at all" to the question "How much does this bother you?"):

a. Question 3: Do you usually have a bulge or something falling out that you can see or feel in your vaginal area?

G. BASELINE VISIT

Candidates will be approached for enrollment in a manner consistent with local IRB requirements and will be consented and enrolled in the study with verbal and written consent. Once eligibility is confirmed, baseline information will be obtained, which will include Demographics, Medical History, Physical Examination, and baseline patient-reported outcome (PRO) forms.

Demographics and Medical History

- Age, race/ethnicity, marital status, education
- Obstetric history (vaginal parity)
- Prior surgical treatment of pelvic organ prolapse or urinary incontinence
- Estrogen status
- Prior treatment of pelvic organ prolapse or urinary incontinence
- Smoking
- Diabetes
- Urinary tract infection history
- Current non-pain medication use including hormonal therapy, antibiotics for UTIs or pelvic floor infections, lower urinary tract medications, and medications that may impact healing and bowel function medication

Surgery should be scheduled and performed within 4 months of consent. If more than 4 months transpires before surgery, a protocol deviation form will be completed.

H. RANDOMIZATION/MASKING

H.1. Randomization

After eligibility is determined and consent is obtained, randomization will occur. Ideally, the time from randomization to surgery will be no longer than 6 weeks (42 days). This time interval will be tracked to determine if delay from randomization to surgery ultimately impacts entry into study represented by those patients undergoing the index surgical procedure. If more than 6 weeks transpires between randomization and surgery, a protocol deviation will be completed. If another visit (i.e. preoperative visit) occurs after randomization, the surgeon should continue to mask the patient to the details of the randomized apical procedure until after completion of the surgery. Randomization in the operating room is not feasible because of the unique equipment to perform laparoscopic and robotic sacral colpopexy. Often robotic rooms are in high demand and need to be reserved and utilized when scheduled. If surgery is not scheduled within 6 months after randomization due to patient-specific reasons unrelated to the masked treatment assignment, the patient may be discontinued from the trial.

The randomization will occur in a ratio of 1:1:1 for each treatment arm with an equal chance of being randomized into each treatment group. While the potential exists to perform a 2:2:1 (SC:TVM:NT) randomization scheme given the prior reported evidence using composite outcomes, the working group believes that this scheme would significantly increase patient confusion in counseling for the study and may impact investigator equipoise. In addition, this

randomization schema would result in unequal group size, making evaluation of adverse events more difficult and potentially unbalanced between groups.

On April 16, 2019, the FDA ordered the removal of transvaginal mesh products including Uphold LITE from the market. The PFDN Steering Committee, with approval from NICHD and the DSMB, halted study enrollment for new patients and halted randomization into the TVM arm. At the time, there were 344 completed surgeries and 18 remaining consented or randomized participants who were awaiting surgery. Remaining patients that were randomized to TVM will be re-randomized to receive one of the two remaining arms (SC and NT). This randomization will occur in a ratio of 1:1.

Randomization will be performed using permuted blocks with a block size that is known only to the DCC and will be stratified by site and age category (< 65 and ≥ 65). For each participant, the web-based system will determine 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 will have access to the randomization table to minimize the risk of selection bias.

H.2. Masking of Randomized Intervention

The participant will remain masked until after surgical repair. Beginning after April 18, 2019, the pending participants who have not undergone surgery will be notified that they will not be randomized into the TVM arm given that this arm is closed at this time. These participants will remain masked to their surgical randomization (SC and NT) until after their surgical repair. Those participants receiving sacral colpopexy will have abdominal incisions, making masking for this technique impossible. Because masking is impractical for the sacral colpopexy arm, the unmasking of the two vaginal arms will occur postoperatively. Given that the primary outcome is based primarily on outcome measures obtained by a masked examiner, unmasking of the participants should not bias the outcomes.

The study surgeon is providing clinical care to enrolled participants, thus masking the surgeon to treatment allocation or participant symptoms is not practical or feasible, other than the allocation concealment prior to surgical randomization.

To minimize biases, follow-up POP-Q measures and complications identified via a physical exam will be obtained by co-investigators or study nurses who are masked to the treatment group. Given the masked follow-up, assessment of efficacy outcomes will not occur until the 6-month visit and participants who all have had prior hysterectomy present with abdominal incisions should not risk unmasking. The masked examiner should not inquire about surgical type and the participant should be instructed not to discuss with the masked examiner. Any participant‘s concerns with details and specifics of the surgery should be forwarded to the participant’s surgeon. We realize that unmasking may occur. If masking occurs, the site should complete a protocol deviation.

Table 3. Masking Summary

Masking	Sacral Colpopexy Intervention	Vaginal Mesh Intervention	Native Tissue Intervention
Participant	Preop only	Preop only	Preop only
Study Coordinator or Study Nurse	No	No	No
Telephone Interviewer (if applicable)	No	No	No
Study Surgeon	No	No	No
Anatomic Evaluator	Yes	Yes	Yes

I. APPOINTMENT SCHEDULING

Routine clinical practice postoperative visits will take place during the 12 week postoperative period. Study data will only be collected at a study visit at 6 weeks to assess for:

1. Urinary function including duration of postop catheterization and de novo voiding dysfunction rates. Post void residual will be assessed by catheterization or bladder scan at 6 weeks. De novo voiding dysfunction will be defined as PVR > 150 ml that was not present preoperatively.
2. De novo incontinence rates assessed by the adverse event (AE) survey.
3. Mesh-related complications: mesh exposure in the vagina or mesh erosion into another organ and the classification of the intervention:
    a. None or non-surgical medical intervention only
    b. Minor or intra-office surgical intervention
    c. Outpatient surgery
    d. Inpatient surgery
4. Rates, location, and severity of pelvic pain using the modified Surgical Pain Scale that has demonstrated validity and responsiveness in OPTIMAL and SUPeR trials, pain medication use (during 72 hours prior to completion of the Body Part Pain Score assessment), AE survey, and Body Part Pain Score assessment.
5. Pelvic infection:
    a. Perioperative infections defined as requiring treatment
    b. Urinary tract infections based on clinical judgment or confirmation of a culture proven by lab criteria (also includes empiric antibiotic treatment for symptoms thought to be secondary to UTI)
    c. Vaginal infections determined by a physician using clinical or radiologic indicators to be uncommon to vagina and requiring treatment
6. Neuromuscular problems (including groin, buttock and leg pain) with the use of the Body Part Pain Score assessment. This assessment is meant to capture new or worsening pain associated with the surgical procedure. We realize that lower back pain and sciatic nerve pain may be chronic in nature.
7. Vaginal scarring, vaginal shortening, de novo or worsening dyspareunia with AE survey.

Subsequent study visits will occur at 6-month intervals for up to 60 months for collection of study measures. In addition to the measures discussed above, anatomic assessment by

masked examiner will occur every 6 months, along with patient reported outcome forms outlined in the timeline that will be completed at the 6-month visit, 12-month visit, and then annually thereafter. The Decision Regret and Satisfaction Decision Scales will be completed annually beginning at 12 months through the 36-month visit. Starting with the 6-month visit, the primary outcome measures (PFDI-20 Question 3, POP-Q, AE assessments) will be collected at 6-month intervals.

Non-pain medication use, including hormonal therapy, antibiotics for UTIs or pelvic floor infections, lower urinary tract medications, and medications that may impact healing and bowel function medication, will also be collected at each study visit.

J. INTERVENTIONS – SURGICAL INTERVENTIONS

J.1. Surgeon Experience and Certification

Experience

The study surgeon is responsible for meeting the experience requirements, is the surgeon of record, and will be present for key portions of the procedure. To reduce bias related to surgical experience, surgeons should be experienced with all three procedures performed in this study. For sacral colpopexy arm, surgeons need to be experienced with the sacral colpopexy approach they will be performing (open, laparoscopic, or robotic). For the native tissue arm, surgeons need to be experienced in either SSLS and/or USLS performed for post-hysterectomy vaginal vault prolapse. For the apical TVM arm, surgeons need to be experienced with the Uphold LITE procedure. Certification criteria ensure that all study surgeries are performed by surgeons who are well trained on procedures for both arms to assure study validity, while at the same time establishing standards for the trial that allow results to be generalized to the population of urogynecologic surgeons likely to perform these surgeries in the future.

Certification

All surgeries will be performed by certified surgeons. Surgeon certification will require an attestation by the surgeon signed off by the site PI. It will require the following requirements:

FOR SC 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® technique.
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. Performance of, or has received hands-on proctoring on at least 5 Uphold® procedures for uterovaginal prolapse or cuff-vaginal prolapse for the technique that he/she will be performing. Surgeons who meet all the criteria except the Uphold LITE® procedure experience criteria may enroll participants in the ASPIRe study; however, if the participant randomizes to the apical TVM arm, the surgery will be proctored by a certified study surgeon. This certified surgeon will be scrubbed in and provide hands-on supervision for the anterior dissection, Capio placement of the mesh arms, tensioning parts of the procedure, and incision closure. The certified proctoring surgeon will be the study surgeon of record and takes full responsibility for the performance and the quality of the procedure. The procedure may be counted as a proctored procedure for the other surgeon.
5. Prior to signing off on certification for each site's surgeon, the site PI will review these 5 cases for any Uphold® procedure-related complications and may request additional proctoring or experience before approving certification of that surgeon.

Surgical Education and Monitoring

At baseline, all study surgeons will provide data on their training, surgical volume, and length of time in practice. On a quarterly basis, all study surgeons will provide the number of post-hysterectomy apical suspensions that they performed outside of the ASPIRe study. Given that SSLS/USLS and ASC are commonly performed, written instruction on the standardized procedure will be available outlining key study points. A DVD illustrating essential components of the Uphold LITE technique for post-hysterectomy POP surgery will be made available and distributed to each participating surgeon along with a detailed written description of the technique and guidelines for concurrent procedures. The DVD and written material will be reviewed and discussed at an in-person PFDN Steering Committee meeting at a time shortly before enrollment begins. Each Principal Investigator at the clinical sites will be responsible for reviewing and discussing the DVD and written materials with participating surgeons at his/her site (before enrollment begins).

Certified Surgeons as Teachers

All sites in the PFDN are teaching institutions and have accredited fellowship programs in Female Pelvic Medicine and Reconstructive Surgery. Residents and fellows may assist with surgery for ASPIRe participants, similar to standard institutional practices. The certified surgeon is always the surgeon of record for the study and takes full responsibility for the performance and the quality of the procedure. The certified surgeon will be scrubbed in and will perform (or provide hands-on supervision) of the procedure. The certified surgeon assumes full responsibility for assuring proper surgical technique and study standardization of the apical procedures.

J.2. Description of Surgical Interventions

J.2.a. Sacral Colpopexy

The technique for SC 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.

1. Mesh:
    a. Standardize mesh characteristics: knitted, large pore (≥ 1800 microns), light weight (≤ 42 g/m2), high porosity (≥ 60%) monofilament polypropylene mesh (no greater than GyneMesh™) will be allowed. See table for comparison. The specific mesh product will be tracked in data forms.
    b. Y-mesh or two separate arms will be allowed. The two arms may be attached using suture per surgeon's choice.
    c. No xenograft or allograft products.
    d. No collagen coated mesh.
    e. Mesh type and configuration will be tracked.
    f. The length of the anterior, posterior, and sacral arms implanted will be recorded in the surgeon's report form.
    g. No minimum mesh length is required and is at surgeon's discretion.
2. 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 and usual practice. No self-locking sutures will be allowed.
    a. Standard suture: While suture types vary across sites, the protocol has standardized the suture type to minimize potential for suture exposure and erosion. Delayed (maxon/pds) or Permanent (prolene/surgipro) monofilament absorbable suture will be used for attachment of mesh to the vagina.
    b. A minimum size of 2-0 suture is required (0 or 2-0). Given the reports of increased suture erosion, Gortex and braided permanent (Ethibond) suture will not be allowed for vaginal attachment.
3. 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 anchor/tacks should be used to attach the mesh. The location will be tracked on the intraoperative data form.
    a. Note: There is no scientific evidence demonstrating improved efficacy or safety with the use of suture or anchor/tacks for sacral attachment. Therefore, either method will be allowed and tracked on the intraoperative data form.
4. Peritoneal closure should be performed in usual fashion.

Table 4. Physical Characteristics of Commonly Used Prolapse Meshes

	Vendor	N	Weight g/m²	Pore Size (mm)	Porosity (%)	Stiffness (N/mm)
Gynemesh PS	Ethicon	4	42	2.47	62	0.29
Alyte Vag Flap	Bard	5	18	2.78	75	0.16
UltraPro* (aka Artisyn)	Ethicon	4	57 (31)	2.5 (3.5)	68 (68)	0.26 (0.01)
Restorelle Y	Coloplast	4	19	1.80	78	0.18
Novasilk	Coloplast	4	19	1.53	67	0.072
Upsylon Y-Mesh Uphold LITE	Boston Sci	Company specs	25	2.8		0.53
Polyform	Boston Sci	4	40	1.77	56	0.13
IntePro Lite used in Elevate-AA	AMS	4	26	2.4	68	0.071

*Values in parentheses represent UltraPro with absorbable component (poliglecaprone 25) absorbed

J.3. Native Tissue Repair

J.3.a. Sacrospinous Ligament Suspension (SSLS)

The SSLS procedure used for this protocol is a modification of the Michigan 4-wall technique originally described by Morley and DeLancey. [45] This modification was performed in the OPTIMAL trial.

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. The placement of sacrospinous ligament stitches will be performed in such a way as to avoid neurovascular and ureteral compromise.
4. Two permanent and two delayed absorbable (4 sutures total), 0 or 2-0 mono-filament stitches must be placed in the left OR right ligament. Bilateral procedures are not permissible.
5. 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.
6. 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.
7. Other aspects of the procedure will be left to the surgeon’s discretion, such as management of enterocele, will be recorded.

J.3.b. Uterosacral Ligament Suspension (USLS)

The USLS procedure used in this protocol is a modification of the technique described by Shull. [46]

1. USLS is performed through a vaginal incision.
2. The placement of uterosacral ligament stitches will be performed in such a way as to avoid neurovascular and ureteral compromise.
3. 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.
4. The use of a pulley stitch is allowed.
5. No plication of the uterosacral ligaments across the midline or culdoplasty is allowed.
6. Other aspects of the procedure will be left to the surgeon's discretion such as management of enterocele will be recorded.
7. In the event that clinical circumstances prohibit safe/effective completion of the planned procedure, the preferred back-up procedure is a SSLS as described above. In the unlikely 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.

J.4. Apical Transvaginal Mesh: Uphold LITE Procedure

The Uphold LITE procedure used in this protocol is a modification of the technique described by Vu. [47]

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 SSL will be allowed.
3. Blunt or sharp dissection to approach the sacrospinous ligament extraperitoneally.
4. After confirmation of the location of the ischial spine, the tapered lead and mesh assembly will be delivered into the SSL 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 allowed as indicated with 0 or 2-0 delayed absorbable mono-filament 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.
11. Placement of a vaginal pack and Foley catheter at surgeon's discretion.

J.5. Other Procedures and Operative Rules

1. Cystoscopy with assessment of ureteral function will be performed at the end of the procedure after all vault suspension sutures are tied, after the TVM straps are adjusted/anchored, and after tensioning of mesh for sacral colpopexy, and is required as a standard part of the surgical procedure.
2. Prophylaxis against deep vein thrombosis is required for all participants. The method may be chosen by each surgeon.
3. Preoperative intravenous antibiotic prophylaxis is required as part of the surgical procedure. The details (choice of antibiotic, dose, etc.) will be determined by each surgeon.
4. All concomitant non-index surgical procedures will be recorded on surgeon's form. This will include planned and performed procedures. The surgeon has the discretion to alter from this preoperative plan as necessary to achieve the desired anatomic result. Any such alterations must be recorded.
5. Anterior and posterior colporrhaphies will be performed at the discretion of the operating surgeon such that points Aa, Ba, Ap and Bp are less than or equal to -1 cm at the end of the procedure (i.e. anterior and posterior vaginal points located at least 1 cm above the hymen) at the end of the procedure. Colporrhaphies, when performed, will be performed with 2-0 or 0 delayed absorbable sutures.
6. Surgery for stress urinary incontinence: Stress continence outcomes are not a primary outcome in this study and it is recognized that there is evidence to support universal or selective use of mid-urethral slings in the setting of open sacral colpopexy and vaginal operations for prolapse. Therefore, concomitant full-length transobturator or retropubic mid-urethral slings will be allowed per the discretion of the surgeon. The placement of a mid-urethral sling should not have an effect on the primary outcome because tension-free vaginal tape has been shown to not provide additional distal anterior vaginal wall support for patients undergoing total mesh colpopexy or laparoscopic colpopexy. [48] The use of retropubic urethropexy at the time of open sacral colpopexy has been described in women without stress urinary incontinence to lessen the risk of postoperative stress urinary incontinence; however, an association of increased anatomic POP failures with those participates who underwent a retropubic urethropexy was identified in this trial. [17] Given the association with retropubic urethropexy with worsening anatomic support and that midurethral slings have not been associated with worsening or improved anatomic support, mid-urethral slings either full-length transobturator or retropubic mid-urethral will be used across all three study groups.

K. OUTCOME VISITS

Outcome visits will occur every 6 months up to a maximum of 60 months. At each of these visits, instruments assessing the primary and secondary outcomes will be administered and a physical exam will be performed to assess anatomic (POP-Q) results, to evaluate for mesh exposures and erosions, and to ask about bulge symptoms (PFDI-Q3) and retreatment so that the primary outcome and safety measures will be assessed. At 6, 12, 24, 36, 48, and 60 months secondary outcome measures will be administered. All women will continue to be

followed through the end of the study, including those who seek alternative treatment or retreatment to ensure that all safety/adverse events are captured. See Timeline Table 5.

Table 5. Timeline of Events

TIMELINE OF MEASURES														
MEASURE	SCREEN	BASE LINE	PERI OP	6 WK	6M	12 M	18 M	24 M	30 M	36 M	42 M	48 M	54 M	60 M
Window (+/- wk)				-1wk / +2wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks
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*				Q 2 weeks if need for continuous catheterization post 6-Week Visit										
Functional Activity Scale		X			X	X		X		X		X		X
Surgical Pain Scale		X		X	X	X		X		X		X		X
Body Part Pain Score		X		X	X	X		X		X		X		X

TIMELINE OF MEASURES														
MEASURE	SCREEN	BASE LINE	PERI OP	6 WK	6M	12 M	18 M	24 M	30 M	36 M	42 M	48 M	54 M	60 M
Window (+/- wk)				-1wk / +2wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks
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	
PFIQ-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				
*If 6 Week Post-Operative Visit indicates that participant requires continued catheterization, complete this every 2 weeks until catheterization ends														

L. DESCRIPTION OF OUTCOME MEASURES

The following outcome measures will be collected at baseline, 6 months, 12 months, and then every 6 months with the survival analysis approach.

L.1. Primary Outcome Measure

The participant will be considered a treatment failure if any ONE of the following criteria is met:

1. Report of bothersome vaginal bulge symptoms (see definition below), or
2. Retreatment for prolapse (surgery or pessary), or
3. Any prolapse measure (Ba, C, Bp) is beyond the hymen (i.e. > 0 cm).

Bothersome vaginal bulge symptoms = positive response to Question 3 of the PFDI-20: Do you usually have a bulge or something falling out that you can see or feel in your vaginal area? and any degree of bother (i.e. any response other than "not at all" to the question "How much does this bother you?")

L.2. Secondary Outcome Measures

Secondary Aim 1 – Secondary Efficacy Outcomes: These measures will require a statistical analysis plan and will be reported in the primary outcome manuscript.

1. Anatomic: POP-Q point (Aa, Ap, Ba, Bp, C) mean or median (but should be normally distributed)
    - (a) Measures postop in each group
    - (b) Proportion of participants in each group with C > -2/3 TVL
    - (c) Maximum extent of prolapse (defined as leading edge of prolapse – Ba, C, Bp)
2. Functional:
    - (d) Prolapse
        - (i) Patients Global Impression of Improvement (PGI-I) [49]
        - (ii) Mean overall prolapse symptoms using POPDI-6 scores (sub-scale of PFDI-20) [50]
    - (e) Urinary
        - (i) Duration of postop catheterization
        - (ii) Mean UDI-6 scores (sub-scale of PFDI-20) [50]
        - (iii) De novo voiding dysfunction rates
        - (iv) De novo incontinence rates
            1. Stress
            2. Urge
            3. Mixed
    - (f) Sexual/Body Image

1. Mean PISQ-IR [51] and BIPOP scales [52]
2. Rates of de novo dyspareunia

(g) Bowel – bowel function using CRADI-8 scores [50]

(h) QOL

(i) General SF-12 scores and sub-scales [53]

(ii) Pelvic QOL – mean PFIQ score [50]

(iii) Katz ADL (ref) (baseline only)

(iv) Functional Activity Scale (ref)

3. Regret/Satisfaction:

(i) Regret with Decision Regret Scale (DRS-PFD) [54]

(j) Satisfaction with Decision Scale (SDS-PFD) [54]

Secondary Aim 2 – Safety: These measures will require a statistical analysis plan and will be reported in the primary outcome manuscript.

1. Intraoperative safety: group comparisons of mean operative time, estimated blood loss, blood transfusion, intra- and postoperative complications categorized using a modification of the Dindo Classification. [55]
2. Adverse events – mesh-related complications: mesh exposure in the vagina or mesh erosion into another organ and the classification of the intervention:

(a) None or non-surgical medical intervention only

(b) Minor or intra-office surgical intervention

(c) Outpatient surgery

(d) Inpatient surgery

3. Other complications possible in all arms:

(a) Rates of pain captured from the modified Surgical Pain Scale [56], pain medication use (during 24 hours prior to completing Body Part Pain Score), and location of pain with Body Part Pain Score.

4. Pelvic infection

(a) Perioperative infections

(b) Urinary tract infections

(c) Vaginal infections with flora uncommon to the vaginal canal

5. De novo vaginal bleeding, atypical vaginal discharge, fistula formation, neuromuscular problems (including groin, buttock and leg pain).
6. 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).
7. Rates of vaginal scarring, defined as de novo scar requiring medical or surgical intervention.

8. Rates of vaginal shortening (TVL < 6 cm), de novo dyspareunia, and worsening dyspareunia with AE survey.

Secondary Aim 3 – Predictors of Poor Outcomes: Assess common factors believed to be associated with surgical treatment failures including:

1. Advanced prolapse
2. Age
3. Obesity
4. Smoking
5. Use of supplemental estrogen
6. Previous POP surgery

Secondary Aim 4 – Body Image: Given the concerns with the impact of mesh placement and vaginal prolapse on body image, body image scales will be obtained and compared between groups.

Body image is how a woman feels (her perceptions and attitudes) about her body. [57] Body image likely plays a role in the decision for treatment for pelvic organ prolapse and a women's satisfaction with treatment. The Body Image Scale (BIS) was originally developed and validated to measure changes in body image in women treated for breast cancer. [58] Jelovsek et al. modified the BIS and compared women with advanced prolapse and a cohort of women with normal support. [59] Other studies have evaluated the impact of body image, sexual function, and prolapse in large multi-center cohorts undergoing surgical and non-surgical treatment of POP. [60, 61] Lowder et al. compared a cohort of women planning surgery and controls with normal support and demonstrated an improvement in body image scores after surgery and an association between prolapse and sexual function. [62] While the BIS scale has been used in the assessment of body image in a number of studies, the scale was not developed with patient input and did not undergo rigorous validation in a prolapse population. Recently, a new body image scale was published that included patient input and underwent rigorous validation. Importantly, this new measure includes evaluation of both partnered and non-partnered women (BIPOP). This new measure, developed by Lowder, will be used and administered based on current partner status. [52]

While we recognize that the groups will not be masked and hence will know whether or not they had mesh placed or underwent a vaginal versus abdominal approach, we believe information on body image changes will be valuable and will also help inform the evaluation in changes in sexual function as measured by the PISQ-IR.

Secondary Aim 5 – Cost–Effectiveness Analysis: The cost-effectiveness analysis will be conducted from a payer perspective and will be expressed as incremental cost required to produce one additional unit of quality-adjusted life year (QALY). Data on each participant's use of medical and non-medical resources related to urologic or gynecologic conditions will be collected during the follow-up period. Direct and indirect costs of the treatment of apical POP with sacral colpopexy, NT surgical repair, or TVM repair, and women's preference for health states for improvement in POP will be estimated.

We plan to capture incremental health care resource use related to study interventions and complications and other prolapse management (such as pessary use or additional surgery).

Costs will be estimated using the resource costing method where medical service use from each study case report form (CRF) is monetized by multiplying the number of units of each medical service by the average unit cost of this service in dollars. This method allows a consistent capture of resource use when costs are incurred across multiple health systems or payers. Detailed CRFs that include the procedures performed (e.g. surgical interventions) and clinical events (e.g. complications, readmissions) will be completed by the study coordinator at study visits. Data from three resource types (physician visits, hospital procedures and admissions, and emergency room visits) will be collected. Cost for each medical service use will be assigned based on national Medicare reimbursement rates, as indicated in the following table. Additionally, we will obtain detailed billing records for a limited number of procedures and hospitalizations in selected study sites (e.g. prolonged admission to the ICU or readmission to the hospital for a surgical complication).

Table 6. Resource Utilization Data Collection and Price Data Source by Utilization Category

Service	Price Weight
Physician Visit	Medicare Reimbursement
Surgical Intervention And Admission Complication Hospitalization – Routine	Medicare Reimbursement Medicare Reimbursement
Complication Hospitalization – Significant ER – Routine Complication	Billing Record – Actual Amount Paid Medicare Reimbursement
ER – Significant Complication	Billing Record – Actual Amount Paid
Subsequent Surgery	Medicare Reimbursement

The SF-6D preference-based utility index algorithm derived from the SF-12 instrument [63] will be used to calculate each participant's utility index at baseline and various follow-up time points based on her responses to the SF-12 questionnaire. The SF-6D focuses on seven of the eight health domains covered by the SF-12: physical functioning, role participation (combined role-physical and role-emotional), social functioning, bodily pain, mental health, and vitality). This instrument has been previously used in women with urinary incontinence. [64] These data will be used to compare change in QALYs between the two treatment groups. We are choosing to use a general scale to calculate change in utilities (rather than condition-specific) to allow for comparison of cost-effectiveness results with other interventions and diseases. Because the follow-up period for participants spans at least three years, costs and QALYs in the second year and third year of follow-up will be discounted using a 3% discount rate/year.

Differential mean costs and differential mean QALYs between the three treatment groups will be estimated using multiple regression analysis. Specifically, a generalized linear model with appropriate link function (e.g. log-link) and response probability distribution (e.g. gamma distribution) will be used to analyze costs due to the potential skewness and heteroscedasticity of medical expenditure data, while an ordinary least squares regression will be used for analyzing QALY data. The models will account for treatment group, study site, and stratification factors, as well as other characteristics of the participants that are found to differ significantly between the sacral colpopexy, apical TVM, and NT groups. When estimating QALYs, we will also adjust for participants' baseline utility scores to account for potential imbalance in baseline utility between the three treatment groups. [65]

We will calculate the incremental cost-effectiveness ratio (ICER), which is the differential mean costs divided by the differential mean QALYs between the two groups, to assess the additional costs associated with each additional QALY gained. Our base case analysis will be conducted based on participants with complete data. A sensitivity analysis will be conducted to include participants with incomplete data using the multiple imputation method. Non-parametric

bootstrapping resampling technique will be used to derive the 95% confidence interval for the ICER. [66, 67] In addition, cost-effectiveness acceptability curve (CEAC) will be generated to illustrate the likelihood that one treatment is more cost-effective than the other with various ceiling cost-effectiveness ratios.

In the case that a statistically significant difference in changes in utilities (as measured by SF-6D) between the treatment groups is not detected, we plan to conduct supplemental analyses using alternative outcome measures, such as incremental cost per treatment success, incremental cost per POP HRQOL, or incremental cost per satisfaction.

The cost-effectiveness evaluations will be conducted as within-trial comparisons. A decision analytic model will also be developed from trial data to evaluate the trajectory of the cost-effectiveness ratio over a lifetime; assuming an average life expectancy, given the average age of participants at the time of the intervention.

L.3. Exploratory Aim: Global Composite Outcome

While traditional outcomes in POP surgery have focused on anatomic outcomes and retreatments and reoperation for POP [68], more recent studies have included subjective measures in the primary outcome. [21] Complications and adverse events have been considered as a secondary aims under safety outcomes and reported separately. [21, 69-71] While patient centered outcomes have recently been validated in pelvic floor surgery, these outcomes are infrequently included in clinical trials. [72] While adverse events have always been important, the recent FDA warning for vaginal mesh has heightened awareness among patients and surgeons alike. The impact of adverse events on patients' perception of success and failure especially in quality of life surgery, such as POP, is lacking. Successful surgery and adverse events may be defined differently by surgeons and patients based on goals and expectations. [73-75]

Clinical decisions about POP treatment may not always have a clear, preferable option and thus should be made on the basis of an individual woman's preferences and values. Such decisions are informed at a minimum by treatment efficacy and complications to allow the patient to weigh the risks and benefits and consider the tradeoffs associated with treatment. Currently there is minimal information regarding what are the most important complications from the patient perspective. In addition, specific complications will remain subject to an individual woman's values and preferences when she balances information about complications with a successful (or unsuccessful) repair.

Treatment decision regret is regarded as an important endpoint for evaluating decision-making in health care and health states. [76] "Regret" can be defined as a negative cognitive and emotional state derived from comparing one's current state with what it might have been had she chosen a preferred, forgone alternative. [77] Health decisions that result in bad outcomes can lead to regret. [78, 79] Regret over treatment decisions has been associated with complications after prostate cancer surgery [80] and anti-incontinence surgery. [81]

The incorporation of patient input into the interpretation of treatment complications in pelvic floor disorders is in its infancy. It remains critical to include a patient perspective measure in our trials to help assess how complications and negative outcomes are interpreted and valued by patients. The Decision Regret Scale (DRS) [82] and Satisfaction with Decision Scale (SDS) [83] are patient-centered outcome measures that have demonstrated good psychometric properties in numerous patient populations and have been previously adapted and validated for pelvic floor disorders (DRS-PFD and SDS-PFD). [85] It has been shown that patients report

higher regret on the DRS when health decisions are followed by negative outcomes. [82] In a study of post-prostatectomy patients, a poor understanding of treatment complications and experiencing postoperative bothersome bowel, sexual, and physical adverse effects were associated with higher DRS scores. [80] Distress from complications was also associated with significantly higher regret scores. [80] In a study evaluating recall of surgical consent for mid-urethral slings, the number of complications was independently associated with higher decision regret. [81]

The DRS-PFD and SDS-PFD are modified scales that have been validated in women undergoing surgical treatment for pelvic floor disorders. Because there is no "gold standard" for regret or satisfaction, validity of these measures has been supported through hypothesis testing and demonstration of construct validity with other measures and health outcomes, consistent with the original measures. Both have demonstrated face and content validity. They have good internal consistency (Cronbach's alpha 0.88 and 0.95, respectively) and reproducibility (intraclass correlations 0.84 and 0.82, respectively). Larger improvements in the PFDI-20 and PFIQ-7 scores were negatively correlated with the DRS-PFD and positively correlated with the SDS-PFD. Because the two questionnaires measure different constructs, it can be recommended that they be administered together. The DRS-PFD is a 5-item questionnaire with a 5-point Likert response scale, and higher scores indicate a higher degree of regret with the treatment decision. The SDS-PFD is a 6-item questionnaire with a 5-point Likert response scale, and higher scores indicate a higher degree of treatment decision satisfaction.

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-12), PGI-I, and adverse events to determine if a valid and reliable global composite outcome can be developed to give weight to these important factors. Adverse events will be informed by both the patient and physician perspective from other studies conducted by the PFDN, since a patient's perspective of adverse events may vary from the perspective of providers. By using information collected during this study pertaining to regret/satisfaction scales, condition specific scales, utility scales, and adverse events obtained a specified collection points, we hope to develop a global composite outcome that can be used in future trials to balance patient centered outcomes to our current definition of surgical success and failure.

L.3.a Global Composite Outcome Development

This exploratory aim will use questionnaires, and monitoring and grading of adverse events collected in this study to develop a global composite outcome. The following will be analyzed in the development of this aim.

Safety/Adverse Events:

- Severity as assessed by Dindo Complication Scale and/or Common Terminology Criteria for Adverse Events (CTCAE)

Regret/Satisfaction:

- DRS-PFD
- SDS-PFD

Condition Specific Improvement:

- PGI-I

Global Improvement:

- SF-12 and subscales

Although the GCO will not be reported as a secondary outcome, the following points will be considered a priori as a failure in order to develop structure for the exploratory aim and future development of a GCO.

Safety/Adverse Events:

- Dindo Complication Scale Class III and IV and CTCAE Grades 3 and 4

Regret/Satisfaction:

- DRS-PFD (a “strongly agree” or “agree” response to regret Question 2)

Condition Specific Improvement:

- PGI-I (a response of “very much worse” or “much worse”)

Global Improvement:

- SF-12 (worsening of utility scores from baseline)

M. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

M.1. Sample Size/Power Calculations

Sample size calculations were generated under the assumptions that the three study arms are: 1) mesh augmented sacral colpopexy, 2) transvaginal mesh repair, and 3) native tissue repair for vault prolapse. Further assumptions were that the study would have an overall Type I error rate of 0.05, that a randomization ratio of 1:1:1 is preferred for feasibility reasons, and that the Type I error (alpha) would be distributed among the following three hypotheses related to the 3 treatment arms in a way that optimizes sample size and at the same time is scientifically defensible:

- H1: transvaginal mesh is non-inferior to mesh augmented sacral colpopexy [spend alpha of 0.03 using a one-sided non-inferiority test]
    - H1a: transvaginal mesh is superior to mesh augmented sacral colpopexy [spend alpha of 0.03 using a two-sided test of superiority]
- H2: mesh augmented sacral colpopexy is superior to native tissue repair [spend alpha of 0.01 using a two-sided test of superiority]
- H3: transvaginal mesh repair is superior to native tissue repair [spend alpha of 0.01 using a two-sided test of superiority]

The sample size estimates also assume that the primary analyses for each of the three hypothesis tests will be based on a survival analysis model with a 2-year recruitment period and a 3-year follow-up period after the last participant is randomized and that loss to follow-up on each arm will be no more than 5% per year, that the 2-year success rates for mesh-augmented sacral colpopexy and transvaginal mesh repair will be 80%, and that the 2-year success rate for native tissue 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 margins, the analyses two-year 15% margin; this non-inferiority margin corresponds to a hazard ratio of 1.93.

Under the assumptions outlined above, the hypothesis test that drives the sample size is the test on non-inferiority of transvaginal mesh to mesh-augmented sacrocolpopexy. A sample size of 121 participants per arm will provide 85% power to demonstrate non-inferiority under the assumptions outlined above. Assuming that 121 participants will also be randomize to native tissue repair, the overall sample size of 363 participants will provide greater than 93% power to demonstrate that each of the mesh augmented arms is superior to native tissue repair under the assumptions outlined above. Because randomization occurs prior to scheduling the surgery, some randomized patients may not receive surgery as a consequence of patient-related events occurring after randomization. To maintain power for the study, patients who are not treated within 6 months may be discontinued from the trial; enrollment will continue until a total sample size of 363 randomized and treated patients is reached.

After April 18, 2019, the study was closed to new surgeries of transvaginal mesh. The remaining 18 consented or randomized patients will be randomized to receive either sacral colpopexy or native tissue repair in a 1:1 ratio. This modification is expected to have minimal to no impact on the planned statistical power, given that the recruitment period had been extended from 2 years to 36 months (thereby increasing power), and the final sample size of the TVM group will be approximately 95% of the planned size, while the other two study arms are expected to meet or even slightly exceed the planned sample size.

M.2. Analysis Populations

Because randomization occurred prior to scheduling the surgery, some randomized patients did not receive surgery. Also, during surgery some patients were determined by the surgeon to be inappropriate candidates to receive the randomized surgery due to anatomic or other contraindications discovered at the time of the surgery and undeterminable prior to surgery. In these cases, the surgeon selected amongst the other two study surgeries based on physician preference.

Evaluations for superiority will follow a modified intent-to-treat (MITT) approach, and evaluations of non-inferiority will follow a per-protocol approach, which is the customary conservative approach for non-inferiority hypotheses.

To define the MITT population, the intent-to-treat population is modified to remove patients who were randomized but never received surgery due to patient-specific reasons unrelated to the randomized treatment.

The per-protocol population is the subset of the modified intent-to-treat population excluding all major protocol violations related to study treatment including receipt of a treatment other than the randomized treatment.

Safety data will be evaluated for the safety population that will exclude randomized participants who discontinued the study without having surgery and participants who received a non-study surgery rather than one of the three study surgeries. Treatment switchers will be included in the treatment they received.

M.3. Statistical Data Analysis

Both for the overall global test across cohorts and within each of the three cohorts, surgical failure rates will be compared using survival analysis approaches appropriate for interval censored data (e.g. interval censored piecewise proportional hazards models) and secondary outcomes will be reported as rates in each group or as group means and evaluated

with the appropriate parametric or nonparametric statistical tests. We will first conduct a model-based analysis using an appropriate proportional hazards model that examines failure risk as a function of randomized treatment arm, with details of the modelling approach specified after masked data review and documented in the statistical analysis plan prior to data unmasking. As specified in the statement of hypotheses and further detailed in the statistical analysis plan, within each analysis population, this single model will be used to generate four hypothesis tests, as applicable. The first test will compare the hazard ratio of the transvaginal mesh arm to the mesh augmented sacrocolpopexy arm against the hypothesized non-inferiority margin of 1.93, followed by a test of superiority if non-inferiority is shown, while the other two hypothesis tests will compare the hazard ratio of transvaginal mesh and mesh augmented sacrocolpopexy, respectively, to native tissue repair against the hypothesized null ratio of 1.0. All model-based analyses will include terms for the stratification parameters used in the randomization.

A number of secondary outcome measures that include both continuous and binary measures will be collected periodically across the study. To account for missing data associated with differential follow-up time associated with the primary design, appropriate model-based approaches (linear mixed models for continuous outcomes and generalized linear models for binary measures) will be used to compare the effects of treatment. The approach for these secondary analyses will be included in the statistical analysis plan.

M.4. Futility/Stopping Rules

Given the unique nature of a three-arm randomized surgical trial, the Steering Committee initially considered the development of stopping rules for this protocol. The working group also considered the performance of a pilot study, but the disadvantage of enrollment of eligible patients that would not be used in the analysis was believed to offer minimal advantages compared to the development of an ancillary recruitment plan for slow recruitment versus futility/stopping rules for minimal recruitment. After careful consideration, the Steering Committee elected not to have formal stopping rules but to allow the DSMB and Steering Committee to monitor recruitment on a regular basis (similar to other PFDN studies). Thus, enrollment will initially be assessed 6 months after initiating the study. Based on prior PFDN studies, a goal of 20% of total enrollment will be set. If this goal is not obtained, additional non-network sites will be considered from a pool of sites pre-approved prior to this time.

The working group also considered the possibility of having one or more formal interim analyses that would provide for early stopping for a demonstrated efficacy benefit, but rejected that option for two reasons. First, the study is designed to enroll only 121 participants per treatment arm, and the group was concerned that stopping the study with fewer participants than 121 per arm, even with relatively small p-values, might limit the impact of any findings on clinical practice because of the small sample sizes. Second, the hypothesis tests among the 3 arms, with a combination of superiority and non-inferiority hypotheses, will be complicated to explain to the clinical community if all 3 arms enroll to study completion. Stopping one of the arms early and testing two of the 3 hypotheses with a less than full sample and taking the other two arms to completion would complicate the explanation of the study even further. Given the small likelihood of stopping a study early for 2 of the 3 hypotheses, the complications of the approach appear to outweigh any potential benefits.

N. ETHICAL CONCERNS, LIMITATIONS, AND INFORMED CONSENT

N.1. Ethical Concerns

Following the FDA notification on April 16, 2019, the Steering Committee along with the NICHD and DSMB felt that it would be unreasonable to continue with enrollment of patients into the TVM arm of the trial. Thus, the TVM arm was halted at this time. All participants including those who received TVM will continued to be followed as recommended by the FDA and PFDN Steering Committee. Participants who were randomized to receive TVM will be notified of the FDA statement and recommendation for follow up.

Physician bias against vaginal mesh: Physicians may be reluctant to perform vaginal mesh supporting procedure instead of the traditional native tissue apical suspension. Some physicians (and patients) have strong beliefs against the use of mesh, especially in light of the July 2011 FDA warning. Survey results still demonstrate that many AUGS members are performing these procedures, implying that this is still a relevant surgical problem. The mesh used in this study with the Uphold LITE device minimizes mesh load. The mesh exposure rates and complications related to mesh should be low as the mesh load is small, the newer Uphold mesh is even less dense, and it is not placed adjacent to the incision. Furthermore, we will recommend stopping rules if mesh erosion rates requiring OR removal are > 15%. This should be acceptable to surgeon and patient. We believe that this study has equipoise, given the expected similar recovery and morbidity for other procedures. If mesh apical procedures are comparable to mesh anterior compartment procedures, then evidence for equipoise comes from systematic reviews and a RCT, which already support improved anatomic outcomes with mesh in the anterior compartment. The study also has relevance given the continued use of vaginal apical mesh kits (industry source 20K annually). Current recruitment data in the SUPeR trials provides further evidence that we can successfully recruit for an apical TVM trial. The SUPeR study is recruiting participants with primary operations for prolapse, which was considered by some to be more difficult to enroll given the use of TVM as a first line surgical therapy. While not all participants in ASPIRe will have had prior POP repairs, all potential participants will have had prior pelvic surgery. The use of mesh for secondary operations for prolapse is even more accepted by physicians and professional organizations than the use of TVM for primary operations. Including native tissue repairs is important because it is commonly performed in clinical practice for POP repair and there is limited data comparing NT repairs to ASC and apical TVM procedures. In addition, native tissue repairs may perform better in terms of composite outcomes, which are likely to be more relevant to patient satisfaction following apical repair.

Physicians may also be reluctant to use vaginal mesh either because they prefer a native tissue vaginal approach or perform sacral colpopexies in their practice. However, all three study procedures are all performed in usual clinical practice and comprehensive preoperative counseling involve discussion of all three of these treatment options.

Participant bias: Women may have preferences regarding placement of mesh in their surgical repair. We believe evidence-based counseling on the pros and cons of these three options with emphasis on the importance of studying the issue will resolve this. We have heard from various sources that randomization in surgical trials is too difficult or not possible for more than 12 years in both networks and every time we have been able to complete the trial. We think that we will have fewer problems in this country and in this network because of our track record of effective randomization. We believe that in the post-hysterectomy vaginal vault prolapse patients any participant bias especially if they have had a prior POP repair will be even less since many patients elect for mesh placed abdominally for POP in usual practice.

Perception of commercial bias: It is not unprecedented for a NIH funded network to study a specific product (e.g. Botox, Interstim in the PFDN ROSETTA; Uphold LITE in the PFDN SUPeR; Gynecare TVT, TVT-O and AMS Monarc in the UITN TOMUS study). If a non-commercial, home-made mesh bridge device was studied and proven inferior, proponents could argue it was the fault of a non-standardized device. Thus, we are using a standardized Vaginal Mesh Kit (Uphold LITE) and mesh approved for Sacral Colpopexy. After a Steering Committee vote, we have elected not to seek external industry funding, given the large number of company products that can be used in this trial to remove the perception of commercial bias. Given the ability for network surgeons to use multiple products that meet pre-outlined criteria (SC-mesh and TVM- Uphold LITE), we believe that perception of commercial bias is minimized in the ASPIRe study.

N.2. Informed Consent Issues

Patients who are candidates for study participation will be approached for enrollment. Written informed consent will be obtained in accordance with IRB Guidelines. A common template for informed consent will be used by all centers, with modifications allowed to meet the necessary requirements of their institutional human subjects committees.

All patients will be made aware of the risks of transvaginal mesh included in the FDA warning (e.g. mesh erosion, pelvic pain, and dyspareunia) via the study informed consent statement.

N.3. Data and Safety Monitoring Board

The NICHD has established a Data Safety Monitoring Board (DSMB) to oversee this study. Members of the DSMB are independent of the study investigators and include representatives with urology, urogynecology, and biostatistics expertise, and a lay member. The DSMB will have regularly scheduled meetings, either in person or by teleconference. The Chair may request to meet more frequently.

This protocol will be approved by the DSMB prior to initiation of recruitment. The DSMB will also monitor study progress and will have the ability to recommend that the trial be stopped for safety, futility, or efficacy as outlined in the paragraphs below.

At each regularly scheduled meeting, the DSMB will review enrollment and participant safety information and will have the authority to recommend to the NICHD Director that the study be stopped for either safety or futility. While the safety guidelines described in Section M.4. will be considered by the DSMB in their deliberations about study safety and futility, final stopping criteria will be established by the DSMB.

N.4 Complication Monitoring

Groups will be compared for rates of “important complications”. The definition of “important complication” is:

- Any Grade IIIb or greater Dindo complication, which will also include any intervention under a regional anesthetic. These concurrent or subsequent operating room interventions include but are not limited to: mesh removal, ureteral repair, abscess drainage, small bowel obstruction and revision of vaginal stricture.
- New onset or worsening dyspareunia preventing vaginal intercourse.

- Intractable pelvic pain, defined as daily pelvic pain after the 6 week postoperative visit, which significantly affects the participant's quality of life requiring ongoing management or is refractory to medical and physical therapy.

The important complication rate will be calculated at 6 month intervals for both groups; as a guideline, the protocol committee considers that a true difference of more than 15 percentage points in the complication rates for the three surgical procedures to represent an important difference between groups. Stopping the study will be considered by the DSMB during regularly scheduled reviews if they find compelling evidence of an important difference based on point and interval estimates of the important complication rates in the three study arms. While the true difference of 15 percentage points or greater can guide the DSMB considerations, final decisions about a magnitude of difference in safety risk that warrants a recommendation to stop the study lie fully within the discretion of the DSMB.

N.5. Adverse Events

Adverse event means any untoward medical occurrence associated with a clinical study in humans, whether or not considered study-related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with study intervention, and does not imply any judgment about causality. Lack of efficacy does not meet adverse event criteria.

Reporting of Adverse Events

Adverse events that occur during the study period (from the time of treatment initiation through the completion of follow-up) will be recorded on designated case report forms. Failure of the study interventions to adequately treat prolapse (failure of efficacy) will be captured by the study endpoints and will not be recorded as an adverse event.

The degree of information collected will vary with follow-up time to minimize participant burden over this period, while ensuring that AE data collected are adequate to allow comparison of the AE risk associated among treatments. The decisions about whether or not to collect an adverse event are based in part on the relationship of the event to the pelvis or to surgery (note that this relationship is different than the relationship to the study intervention).

Guidelines:

1. 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.
2. 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.
3. 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.

Reporting of Serious Adverse Event

Each clinical investigator is responsible for reporting serious adverse events (SAEs) to the IRB at their institution per local IRB requirements, and to the DCC (Data Coordinating Center) within 24 hours of when the clinical site is notified of the event. In accordance with

21CFR312.32, an adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

a. Death,
b. Life-threatening adverse event,
c. Inpatient hospitalization or prolongation of existing hospitalization,
d. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
e. Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an adverse event or that, had it occurred in a more severe form, might have caused death.

Additionally, 21CFR803.1 requires reporting of any required intervention to prevent permanent impairment or damage (applies to devices). This should be reported if you suspect that the use of a medical product may have resulted in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.

Any serious adverse events (SAEs) that are deemed related and unexpected will be submitted in a safety report to the DSMB and all participating investigators. Clinical sites will follow local IRB guidelines for submission of any unexpected and related SAEs that occur at both their own site and at other study sites.

Once the SAE is reported to the DCC, it is reviewed by the sponsor and the medical safety monitor (MSM). A SAE summary report is sent to the DSMB. The SAE review process will be documented in the DSMB files.

The DCC summarizes all SAEs and all AEs by randomization group, including events that are not related to the intervention, for the DSMB at each DSMB meeting. In addition, the DSMB report contains accrual and dropout rates. The DSMB will summarize their findings to the sponsor with approval to continue the clinical trial or a recommendation to modify or terminate the trial.

Participant Withdrawal

A participant may be withdrawn from the trial and/or discontinue study treatment as a result of the following:

- At their own request or at the request of their legally acceptable representative.
- If continuation in the trial would be detrimental to the well-being of the participant, in the investigator's opinion.

- If the patient is diagnosed with a condition which is excluded per protocol.
- At the specific request of the sponsor or termination of the study by the sponsor.
- If a randomized patient has not been scheduled for surgery within 6 months of randomization, due to patient-specific reasons unrelated to the randomized treatment.

In the event that a participant withdraws consent before completing the study per protocol, attempts will be made to collect the most recently applicable information and follow AEs/SAEs to resolution. If a participant discontinues treatment but does not withdraw consent, all attempts will be made to continue follow-up of the participant per protocol.

N.6. Data Sharing

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Pelvic Floor Disorders Network (PFDN) plans to make data generated by PFDN studies available to external researchers in accordance with NIH data sharing policies. Data to be shared include clinical datasets of variables collected via the electronic data capture system, and analysis datasets containing derived variables that would enable a researcher to reproduce published study results. The data will be de-identified to protect study participant confidentiality. PFDN Data Coordinating Center (DCC) statisticians will implement a series of steps to de-identify study datasets in order to minimize the risk of researchers identifying any individuals in the data. This process will be consistent with Health Insurance Portability and Accountability Act (HIPAA), Health and Human Services (HHS) policies for protection of human research subjects, and related requirements for protecting participant confidentiality. The PFDN Steering Committee will have the opportunity to review and approve each request for the Network's data prior to release of the data. Because public data sharing may not have been explicitly described in the informed consent forms used to consent study participants, site IRBs will need to determine whether the study data can be shared after being de-identified.

N.7. Addendum to the Protocol:

The following communication was shared with local IRBs regarding removal of the transvaginal arm in April 2019:

The FDA issued a public notice on Tuesday, April 16, 2019, ordering all manufacturers of surgical mesh products for transvaginal repair of prolapse to stop selling and distributing their products in the US immediately. The remaining manufacturers producing transvaginal mesh kits are Boston Scientific, that markets the Uphold LITE Vaginal Support System and Xenform Soft Tissue Repair System, and Coloplast, that markets Restorelle DirectFix Anterior. In the news release, the FDA determined that the manufacturers, Boston Scientific and Coloplast, have not demonstrated a reasonable assurance of safety and effectiveness for these devices, which is the premarket review standard that now applies to them since the agency reclassified them as class III (high risk) in 2016. Boston Scientific and Coloplast have 10 days to notify the FDA of their plans to remove their products from the market.

The FDA recommends that "women who have had transvaginal mesh placed for the surgical repair of POP should continue with their annual and other routine check-ups and follow-up care. There is no need to take additional action if they are satisfied with their surgery and are not having complications or symptoms. Patients should notify their health care professionals if they have complications or symptoms, including persistent vaginal bleeding or discharge, pelvic or groin pain or pain with sex. They should also let their health care professional know if they

have surgical mesh, especially if they plan to have another surgery or other medical procedures. Women who were planning to have mesh placed transvaginally for the repair of POP should discuss other treatment options with their doctors."

Implications for the PFDN ASPIRe Trial

The FDA's decision could impact ASPIRe participants who had been previously scheduled to receive a transvaginal mesh surgery but have not yet had the surgery. The ASPIRe trial noted above randomizes women to one of 3 types of surgeries, one of which uses the Uphold™ LITE mesh, a *Boston Scientific* product. The FDA's decision is based on recommendations from the FDA Advisory Panel who met in February 2019, and review of data submitted by the manufacturers, not the conduct of ASPIRe study.

The Pelvic Floor Disorders Network (PFDN) have had discussions with the FDA and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) leadership about how to handle ASPIRe patients who have previously scheduled transvaginal mesh repair surgeries. FDA and NICHD leadership informed the PFDN that we may continue to perform transvaginal mesh repair for the remaining ASPIRe participants, if we chose to do so.

The target enrollment for ASPIRe is 363 randomized and treated women. To date, 344 women have completed surgery, 12 women have been randomized and have been scheduled for surgery, and 6 women have been consented and are awaiting randomization. The FDA's decision impacts the 18 ASPIRe participants who have not yet had surgery.

The PFDN principal investigators and NICHD representatives convened on April 18, 2019 to discuss the FDA's notice and made the following decisions:

1. No further transvaginal mesh surgeries will be performed on ASPIRe participants.
2. ASPIRe participants who have been randomized to transvaginal mesh repair and are awaiting surgery will be re-randomized to one of the other two surgical arms, sacral colpopexy or native tissue repair.
3. Consented ASPIRe participants who have not yet been randomized will be randomized to one of the other two surgical arms, sacral colpopexy or native tissue repair.
4. All ASPIRe participants who have not had surgery will be informed that they will be randomized to one of the two other surgical arms. Each local IRB will make recommendations on an acceptable process for reconsenting the participants. Given that the only change in the consent is removal of one of the treatment arms (transvaginal mesh), local IRB may consider verbal and written consent with documentation of the modification to a two-arm randomization or to reconsent with a new modified IRB approved written consent.
5. No new patients will be enrolled in the ASPIRe trial.

The Data Safety & Monitoring Board (DSMB) for the PFDN was notified of the FDA's decision and the PFDN's decisions for moving forward with the ASPIRe trial on Thursday, April 18, 2019. The DSMB has been privy to ongoing postoperative adverse event data for the ASPIRe trial and will continue to actively monitor safety events.

In light of the conclusions above, the ASPIRe protocol team will revise the consent, as required by individual IRBs, to state that participants who have not had surgery will be informed that they will be randomized to one of the two other surgical arms. An amended protocol and a revised consent form will be submitted to local IRBs as required by individual IRBs. ASPIRe participants who have already had study surgery will be notified of the FDA's decision and told

that the PFDN plans to continue to follow all ASPIRe participants, including those who have had mesh repair, through 5 years and will continue to monitor all patients for safety events.

This communication to our local site IRB's has been approved by the *Eunice Kennedy Shriver* NICHD PFDN Project Scientist and the PFDN Principal Investigators and Protocol Team investigators for the "ASPIRe" studies at UC San Diego, Kaiser San Diego, University of Alabama at Birmingham, University of Pennsylvania, University of Pittsburgh, Brown University, Duke University, University of Texas Southwestern Medical Center, Cleveland Clinic, and the University of New Mexico.

REFERENCES

1. Boyles, S.H., A.M. Weber, and L. Meyn, *Procedures for pelvic organ prolapse in the United States, 1979-1997.* Am J Obstet Gynecol, 2003. **188**(1): p. 108-15.
2. Swift, S.E., *The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care.* Am J Obstet Gynecol, 2000. **183**(2): p. 277-85.
3. Summers, A., et al., *The relationship between anterior and apical compartment support.* Am J Obstet Gynecol, 2006. **194**(5): p. 1438-43.
4. Hsu, Y., et al., *Anterior vaginal wall length and degree of anterior compartment prolapse seen on dynamic MRI.* Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(1): p. 137-42.
5. *Serious complications associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence*. October 2008; Available from: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.html.
6. Clark, A.L., et al., *Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence.* American journal of obstetrics and gynecology, 2003. **189**(5): p. 1261-7.
7. Olsen, A.L., et al., *Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence.* Obstetrics and gynecology, 1997. **89**(4): p. 501-6.
8. Jelovsek, J.E., C. Maher, and M.D. Barber, *Pelvic organ prolapse.* Lancet, 2007. **369**(9566): p. 1027-38.
9. Clemons, J.L., et al., *Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery.* Female pelvic medicine & reconstructive surgery, 2013. **19**(4): p. 191-8.
10. Sokol, A.I., et al., *One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse.* American journal of obstetrics and gynecology, 2012. **206**(1): p. 86 e1-9.
11. Menefee, S.A., et al., *Colporrhaphy compared with mesh or graft-reinforced vaginal paravaginal repair for anterior vaginal wall prolapse: a randomized controlled trial.* Obstetrics and gynecology, 2011. **118**(6): p. 1337-44.
12. Krlin, R.M., A.M. Murphy, and H.B. Goldman, *Pro: the contemporary use of transvaginal mesh in surgery for pelvic organ prolapse.* Current opinion in urology, 2012. **22**(4): p. 282-6.
13. Maher, C., et al., *Surgical management of pelvic organ prolapse in women.* The Cochrane database of systematic reviews, 2013. **4**: p. CD004014.
14. Siddiqui, N.Y., E.J. Geller, and A.G. Visco, *Symptomatic and anatomic 1-year outcomes after robotic and abdominal sacrocolpopexy.* American journal of obstetrics and gynecology, 2012. **206**(5): p. 435 e1-5.
15. Paraiso, M.F., et al., *Laparoscopic compared with robotic sacrocolpopexy for vaginal prolapse: a randomized controlled trial.* Obstetrics and gynecology, 2011. **118**(5): p. 1005-13.

16. Paraiso, M.F., et al., *Laparoscopic and abdominal sacral colpopexies: a comparative cohort study.* American journal of obstetrics and gynecology, 2005. **192**(5): p. 1752-8.
17. Nygaard, I., et al., *Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse.* JAMA : the journal of the American Medical Association, 2013. **309**(19): p. 2016-24.
18. Nygaard, I.E., et al., *Abdominal sacrocolpopexy: a comprehensive review.* Obstetrics and gynecology, 2004. **104**(4): p. 805-23.
19. Barber, M.D. and C. Maher, *Apical prolapse.* International urogynecology journal, 2013. **24**(11): p. 1815-33.
20. Sung, V.W., et al., *Graft use in transvaginal pelvic organ prolapse repair: a systematic review.* Obstetrics and gynecology, 2008. **112**(5): p. 1131-42.
21. Barber, M.D., et al., *Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial.* JAMA : the journal of the American Medical Association, 2014. **311**(10): p. 1023-34.
22. Feiner, B., J.E. Jelovsek, and C. Maher, *Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: a systematic review.* BJOG : an international journal of obstetrics and gynaecology, 2009. **116**(1): p. 15-24.
23. Diwadkar, G.B., et al., *Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review.* Obstetrics and gynecology, 2009. **113**(2 Pt 1): p. 367-73.
24. Liang, R., et al., *Vaginal degeneration following implantation of synthetic mesh with increased stiffness.* BJOG : an international journal of obstetrics and gynaecology, 2013. **120**(2): p. 233-43.
25. Feola, A., et al., *Deterioration in biomechanical properties of the vagina following implantation of a high-stiffness prolapse mesh.* BJOG : an international journal of obstetrics and gynaecology, 2013. **120**(2): p. 224-32.
26. Rivaux, G., et al., *[Utero-vaginal suspension using a bilateral vaginal anterior sacrospinous fixation with mesh. Preliminary results].* Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie, 2012. **22**(17): p. 1077-83.
27. Vu, M.K., et al., *Minimal mesh repair for apical and anterior prolapse: initial anatomical and subjective outcomes.* International urogynecology journal, 2012. **23**(12): p. 1753-61.
28. Jirschele K, Seitz. A multicenter, prospective trial to evaluate mesh-augmented sacrospinous hyteropexy for uterovaginal prolapse. Int Urogynecol J 2015;26:743)
29. Letouzey V, Ulrich D, Balenbois E, Cornille A, de Tayrac R, Fatton B. Utero-vaginal suspension using bilateral vaginal anterior sacrospinous fixation with mesh: intermediate results of a cohort study. Int Urogynecol J. DOI10.1007/s00192-015-2748-z
30. Moore RD, Mitchell GK, Miklos JR. Single-incision vaginal approach to treat cystocele and vault prolapse with an anterior wall mesh anchored apically to the sacrospinous ligaments. Int Urogynecol J. 2012 Jan;23(1):85-91. doi: 10.1007/s00192-011-1536-7. PMID: 21866442
31. Stanford EJ, Moore RD, Roovers JP, VanDrie DM, Giudice TP, Lukban JC, Bataller E, Sutherland SE. Elevate and Uterine Preservation: Two-Year Results. Female Pelvic Med Reconstr Surg. 2015 Jul-Aug;21(4):205-10. doi: 10.1097/SPV.0000000000000180. PMID: 26052644
32. Stanford EJ, Moore RD, Roovers JP, Courtieu C, Lukban JC, Bataller E, Liedl B, Sutherland SE. Elevate anterior/apical: 12-month data showing safety and efficacy in surgical treatment of pelvic organ prolapse. Female Pelvic Med Reconstr Surg. 2013 Mar-Apr;19(2):79-83. doi: 10.1097/SPV.0b013e318278cc29. PMID: 23442504
33. Rapp DE, King AB2, Rowe B3, Wolters JP. Comprehensive evaluation of anterior elevate system for the treatment of anterior and apical pelvic floor descent: 2-year

followup. Urol. 2014 Feb;191(2):389-94. doi: 10.1016/j.juro.2013.08.023. PMID: 23973517
34. Lo TS, Tan YL, Cortes EF, Pue LB, Wu PY, Al-Kharabsheh A. Anterior-apical single-incision mesh surgery (SIMS): surgical and functional outcomes at 1 year. J Minim Invasive Gynecol. 2015 Jan;22(1):50-6. doi: 10.1016/j.jmig.2014.07.002. PMID: 25017520
35. Marschke J, Hengst L, Schwertner-Tiepelmann N, Beilecke K, Tunn R. Transvaginal single-incision mesh reconstruction for recurrent or advanced anterior vaginal wall prolapse. Arch Gynecol Obstet. 2015 May;291(5):1081-7. doi: 10.1007/s00404-014-3497-9. PMID: 25280572 *35*
36. Sung VW. Rogers RG. Schaffer JI. Balk EM. Uhlig K. Lau J. Abed H. Wheeler TL 2nd. Morrill MY. Clemons JL. Rahn DD. Lukban JC. Lowenstein L. Kenton K. Young SB. Society of Gynecologic Surgeons Systematic Review Group. Graft Use in transvaginal Pelvic Organ Prolapse Repari: a Systematic Review. Obstetrics & Gynecology. **112**(5):1131-42, 2008 Nov.
37. Altman, D., et al., *Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse.* The New England journal of medicine, 2011. **364**(19): p. 1826-36.
38. Nguyen, J.N. and R.J. Burchette, *Outcome after anterior vaginal prolapse repair: a randomized controlled trial.* Obstetrics and gynecology, 2008. **111**(4): p. 891-8.
39. Maher, C.F., et al., *Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial.* American journal of obstetrics and gynecology, 2011. **204**(4): p. 360 e1-7.
40. Barber, M.D., et al., *Defining success after surgery for pelvic organ prolapse.* Obstetrics and gynecology, 2009. **114**(3): p. 600-9.
41. Swift, S.E., *The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care.* American journal of obstetrics and gynecology, 2000. **183**(2): p. 277-85.
42. Barber, M.D., et al., *Defining success after surgery for pelvic organ prolapse.* Obstet Gynecol, 2009. **114**(3): p. 600-9.
43. Brubaker, L., et al., *Quantification of vaginal support: are continuous summary scores better than POP-Q stage?* Am J Obstet Gynecol, 2010. **203**(5): p. 512 e1-6.
44. Bump, R.C., et al., *The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction.* Am J Obstet Gynecol, 1996. **175**(1): p. 10-7.
45. Morley, G.W. and J.O. DeLancey, *Sacrospinous ligament fixation for eversion of the vagina.* Am J Obstet Gynecol, 1988. **158**(4): p. 872-81.
46. Shull, B.L., et al., *Preoperative and postoperative analysis of site-specific pelvic support defects in 81 women treated with sacrospinous ligament suspension and pelvic reconstruction.* Am J Obstet Gynecol, 1992. **166**(6 Pt 1): p. 1764-8; discussion 1768-71.
47. Vu, M.K., et al., *Minimal mesh repair for apical and anterior prolapse: initial anatomical and subjective outcomes.* Int Urogynecol J, 2012.
48. McDermott, C.D., et al., *The effect of tension-free vaginal tape placement on distal anterior vaginal wall support at the time of laparoscopic sacral colpoperineopexy.* Arch Gynecol Obstet, 2011. **283**(6): p. 1303-7.
49. Yalcin, I. and R.C. Bump, *Validation of two global impression questionnaires for incontinence.* Am J Obstet Gynecol, 2003. **189**(1): p. 98-101.
50. Barber, M.D., et al., *Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders.* Am J Obstet Gynecol, 2001. **185**(6): p. 1388-95.
51. Rogers, R.G., et al., *A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12).* Int Urogynecol J Pelvic Floor Dysfunct, 2003. **14**(3): p. 164-8; discussion 168.

52. Lowder, J.L., et al., *Body Image in Pelvic Organ Prolapse (BIPOP) Questionnaire: Development and Validation.* American journal of obstetrics and gynecology, 2014.
53. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
54. Sung, V.W., et al., *Validation of decision-making outcomes for female pelvic floor disorders.* American journal of obstetrics and gynecology, 2008. **198**(5): p. 575 e1-6.
55. Dindo, D., N. Demartines, and P.A. Clavien, *Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.* Ann Surg, 2004. **240**(2): p. 205-13.
56. Barber, M.D., et al., *Validation of the surgical pain scales in women undergoing pelvic reconstructive surgery.* Female pelvic medicine & reconstructive surgery, 2012. **18**(4): p. 198-204.
57. Cash, T., *The psychology of physical appearance: Aesthetics, attributes, and images*, ed. TF Cash and t PRuzinsky (Eds). New York: Guilford Press.
58. Hopwood, P., et al., *A body image scale for use with cancer patients.* Eur J Cancer, 2001. **37**(2): p. 189-97.
59. Jelovsek, J.E. and M.D. Barber, *Women seeking treatment for advanced pelvic organ prolapse have decreased body image and quality of life.* Am J Obstet Gynecol, 2006. **194**(5): p. 1455-61.
60. Lowenstein, L., et al., *Sexual function is related to body image perception in women with pelvic organ prolapse.* The journal of sexual medicine, 2009. **6**(8): p. 2286-91.
61. Lowenstein, L., et al., *Changes in sexual function after treatment for prolapse are related to the improvement in body image perception.* The journal of sexual medicine, 2010. **7**(2 Pt 2): p. 1023-8.
62. Lowder, J.L., et al., *Body image in women before and after reconstructive surgery for pelvic organ prolapse.* International urogynecology journal, 2010. **21**(8): p. 919-25.
63. Brazier, J.E. and J. Roberts, *The estimation of a preference-based measure of health from the SF-12.* Med Care, 2004. **42**(9): p. 851-9.
64. Hollingworth, W., et al., *Exploring the impact of changes in neurogenic urinary incontinence frequency and condition-specific quality of life on preference-based outcomes.* Qual Life Res, 2010. **19**(3): p. 323-31.
65. McCulloch CE, S.S., *Generalized, linear, and mixed models*. 2001, New York: John Wiley.
66. Efron B, T.R., *An introduction to the bootstrap*. 1993, New York: Chapman and Hall.
67. Subak, L.L., et al., *High costs of urinary incontinence among women electing surgery to treat stress incontinence.* Obstet Gynecol, 2008. **111**(4): p. 899-907.
68. Benson, J.T., V. Lucente, and E. McClellan, *Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation.* Am J Obstet Gynecol, 1996. **175**(6): p. 1418-21; discussion 1421-2.
69. Brubaker, L., et al., *Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence.* Obstet Gynecol, 2008. **112**(1): p. 49-55.
70. Richter, H.E., et al., *Retropubic versus transobturator midurethral slings for stress incontinence.* N Engl J Med, 2010. **362**(22): p. 2066-76.
71. Wei, J.T., et al., *A midurethral sling to reduce incontinence after vaginal prolapse repair.* The New England journal of medicine, 2012. **366**(25): p. 2358-67.
72. Sung, V.W., et al., *Treatment decision-making and information-seeking preferences in women with pelvic floor disorders.* International urogynecology journal, 2010. **21**(9): p. 1071-8.
73. Tevis, S.E. and G.D. Kennedy, *Postoperative complications and implications on patient-centered outcomes.* The Journal of surgical research, 2013. **181**(1): p. 106-13.

74. Gutman, R.E., et al., *The pelvic floor complication scale: a new instrument for reconstructive pelvic surgery.* American journal of obstetrics and gynecology, 2013. **208**(1): p. 81 e1-9.
75. Elkadry, E.A., et al., *Patient-selected goals: a new perspective on surgical outcome.* American journal of obstetrics and gynecology, 2003. **189**(6): p. 1551-7; discussion 1557-8.
76. Smith, R.D., *Is Regret Theory an alternative basis for estimating the value of healthcare interventions?* Health Policy, 1996. **37**(2): p. 105-15.
77. Fernandes-Taylor, S. and J.R. Bloom, *Post-treatment regret among young breast cancer survivors.* Psychooncology. **20**(5): p. 506-16.
78. Hillis, S.D., et al., *Poststerilization regret: findings from the United States Collaborative Review of Sterilization.* Obstet Gynecol, 1999. **93**(6): p. 889-95.
79. Clark, J.A., N.P. Wray, and C.M. Ashton, *Living with treatment decisions: regrets and quality of life among men treated for metastatic prostate cancer.* J Clin Oncol, 2001. **19**(1): p. 72-80.
80. Lin, Y.H., *Treatment decision regret and related factors following radical prostatectomy.* Cancer Nurs. **34**(5): p. 417-22.
81. McFadden, B.L., et al., *Patient recall 6 weeks after surgical consent for midurethral sling using mesh.* Int Urogynecol J. **24**(12): p. 2099-104.
82. Brehaut, J.C., et al., *Validation of a decision regret scale.* Med Decis Making, 2003. **23**(4): p. 281-92.
83. Holmes-Rovner, M., et al., *Patient satisfaction with health care decisions: the satisfaction with decision scale.* Med Decis Making, 1996. **16**(1): p. 58-64.
84. Sung, V.W., et al., Validation of decision-making outcomes for female pelvic floor disorders. Am J Obstet Gynecol, 2008. 198(5): p. 575 e1-6.

APPENDIX A

Table 7. Abdominal Sacral Colpopexy (ASC) Outcomes*

Author	Year	Number of Patients, (number lost to follow-up, if known)	Follow-up (months)	Success Rate (%)	Criteria for Success#	Comments
Addison	1985	56 (2)	39	96	Good vaginal vault suspension in a normal axis	Fascia lata was graft material used for patient with early recurrence 1 patient unimproved as a presacral hemorrhage prevented successful completion of the procedure
Baker	1990	59 (6)	6	100	No complaint of protrusion from the vagina	51/59 patients had postoperative records available, at which time all patients had a well-supported vagina
Snyder	1991	147 (15)	43	93 (108/116)	Lack of major long-term postoperative complications, restoration of functional vagina in the proper axis, and no recurrence of presenting symptoms with at least 6 months of follow-up	Graft attached to the entire length of the vagina in the rectovaginal septum
Imparato	1992	71 (8)	NS	78	Excellent, well-suspended vault on exam	50 had direct attachment of the vaginal apex to the anterior sacrum
				16	Good vault suspension, but asymptomatic vaginal "relaxation"	
Timmons	1992	163	33	99	Good vaginal vault support	The range of success is due to 4 different techniques which were compared
van Lindert	1993	61	32	97	No recurrent vaginal prolapse	8 patients had preservation of the uterus
Grunberge	1994	62 (14)	75.6	94	No moderate vaginal vault prolapse on exam	42 patients had direct attachment of the vagina to the sacral promontory 12 had permanent "suture bridges" 8 had lyodura loops
Lecuru**	1994	203	32.5	86.7-100	Anatomically good results	
				53.3-80.5	Functionally good results	
Brubaker	1995	65 (0)	3	71	No anterior or apical prolapse	63/65 patients had abdominal anterior compartment repair at the time of the sacrocolpopexy

Author	Year	Number of Patients, (number lost to follow-up, if known)	Follow-up (months)	Success Rate (%)	Criteria for Success#	Comments
de Vries	1995	101 (29)	48	32	Fully cured (patient satisfaction based upon questionnaire)	Questionnaires sent to patients to evaluate pain, prolapse-related complaints and functional disorders. Patients indicated symptoms before surgery, > 1 year after surgery, and > 1 year after surgery
				39	Considerable improvement	
				29	No improvement	
Benson	1996	40	60	58 (another 26% of patients had "satisfactory" outcomes)	Patient asymptomatic, vaginal apex supported above the levator plate, no protrusion beyond the hymen	All patients had sacrocolpopexy and paravaginal repair. Results are from a RCT comparing sacrocolpopexy to sacrospinous suspension
Hardiman	1996	80	47	99	No recurrent vault prolapse	
Sullivan	2001	236 (31)	64	100	No recurrence of vaginal or rectal prolapse	Total pelvic mesh repair involved attachment mesh strip between the perineal body and the sacrum, and then attaching two additional strips laterally to the pubis to support the vagina and bladder
				34%	Very satisfied	
				38%	Satisfied	
Occelli**	1999	271 (54)	66	97.7	Cured for prolapse	
Patsner	1999	175 (0)	≥ 12	97	No "mesh failures"	
Sze	1999	56 (9)	23	81	No recurrent prolapse to or beyond the hymen	All 9 patients with recurrent prolapse were symptomatic
Lo	1998	52 (not clear)	25	94	No prolapse > Stage II	Results are from a RCT comparing sacrocolpopexy to sacrospinous ligament suspension
Collopy	2002	89 (0)	56.7	100	No recurrence of rectal or vaginal vault prolapse	All had concomitant culdoplasty
Culligan	2002	245	61.2	85	Any POP-Q point ≥ 2	No apical failures observed
Lefranc	2002	85 (0)	126 (median)	90.6	No relapse of any prolapse	All patients without preoperative SUI had a prophylactic Burch procedure done
Lindeque	2002	262 (0)	≥ 16	99	No vaginal vault prolapse	1/3 failures due to graft detachment from vagina
Medina	2002	97 (1)	19	90	< Grade I prolapse	Etiology of 1 failure was graft detachment from the vagina (etiology of other 4 unknown)
Brizzolara	2003	124	36	98	No recurrent vault prolapse	

Author	Year	Number of Patients, (number lost to follow-up, if known)	Follow-up (months)	Success Rate (%)	Criteria for Success#	Comments
Podratz	1995	50 (6)	70	70	Asymptomatic (including no incontinence) and durable repair by exam	
Hilger	2003	69 (31)	164	74	Subsequent POP operation or a positive response to Question 5 on the PFDI***	
Maher{	2004	47 (1)	24	76% objective 94% subjective	Objective: No POP beyond halfway point Subjective: No symptoms of POP	Results are from a RCT comparing sacrocolpopexy to sacrospinous ligament suspension
Higgs	2005	148		97	No recurrent vault prolapse	24% required recurrent SUI surgery
				59.4	< Grade 1 prolapse	
				78	No prolapse symptoms	
Brubaker	2008	322 (302)	24	56	< Stage 2 prolapse	CARE Trial 2 year follow-up; Reoperations for prolapse occurred in 6 (2%)
				98	≤ Stage 2 prolapse	
				95	POP-Q point C within 2 cm of TVL	
Jeon	2009	57	66 (60-108)	86	< Stage 2 prolapse	Major complication requiring reoperation or intensive care developed in 12 (21%)
Huebner	2009	78 (53)	NS	83	< Stage 2 prolapse	
Tate	2010	100 (58)	60	77	< Stage 2 prolapse	5 year follow-up of RCT comparing polypropylene to cadaveric fascia; polypropylene demonstrated superior anatomic results (93% vs 62%, p = 0.02) but no difference in symptomatic outcomes
				93	Symptoms of prolapse or bulging	

*Prospective and retrospective cohorts with n > 50 published since 1985, ASC arms of 3 RCTs comparing ASC to sacrospinous ligament suspension. #POP staging systems, if used, are indicated as 'grade' for Baden-walker or 'stage' for POP-Q
NS = not stated; SUI = stress urinary incontinence; RPU = retropubic urethropexy; RCT = randomized clinical trial
**Only abstract reviewed (paper not in English)
***Question 5 on the Pelvic Floor Distress Inventory – "Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?"

Table 8. Uterosacral Vault Suspension Procedures

Year	First Author	No. of Pts.	Mean Follow-up Months (range)	Definition of Anatomic Success*	Anatomic Success – All Segments	Anatomic Recurrence by Segment	Reoperation for Prolapse
1997	Jenkins	50	(6-48)	Not defined	96%	Anterior 4%	None reported
1999	Comiter	100	17 (6.5-35)	Grade 0-1	96%	Apex 4%	4 (4%)
2000	Barber	46	15.5 (3.5-40)	Stage 0/1 or Stage 2 without symptoms	90%	Apex 5% Anterior 5% Posterior 5%	3 (6.5%)

Year	First Author	No. of Pts.	Mean Follow-up Months (range)	Definition of Anatomic Success*	Anatomic Success – All Segments	Anatomic Recurrence by Segment	Reoperation for Prolapse
2000	Shull	289	Not stated	Grade 0-1	95%	Apex 1% Anterior 3.5% Posterior 1.4%	None reported
2001	Karram	168	21.6 (6-36)	Grade 0-1	88%	Apex 1% Anterior or posterior 11%	11 (5.5%)
2003	Amundsen	33	28 (6-43)	Stage 0 or 1	82%	Apex 6% Posterior 12%	None reported
2006	Silva	72	61.2 (42-90)	Symptomatic Stage 2 or greater	85%	Apex 3% Anterior 7% Posterior 14%	2 (3%)
2006	Antovska	32	25 (9-42)	Stage 0 or 1	NR	Apex 0% Anterior	
2007	Wheeler	35	24 (0-46)	Stage 0 apical prolapse	80%	Apex 20%	0 (0%)
2009	De Boer	48	12	Stage 0-1	48%	Apex 4.2% Anterior 47.9% Posterior 14.6%	None reported
2011	Doumouchtsis	42	60	Grade 0 of vaginal vault	84.6%	Apex 15.4%	5 (11.9%)
2013	Barber	188	24	Composite	58.4%		

In summary, uterosacral vault suspension procedures have a low overall recurrence rate of 4%-18%, anterior vaginal recurrence rates of 1%-6% and a reoperation rate of less than 7%. Ureteral injury rates of 1%-11% are reported.

Table 9. Sacrospinous Ligament Suspensions

First Author (year)	Study Design	n	Mean Follow-up Mo. (range)	Definition of Anatomic Success*	Anatomic Success	Anatomic Recurrence by Segment	Reoperation for POP
Morley	Retrospective	92	51.6 (1-132)	Not defined	90%	Apex 4% Anterior 6%	4 (5%)
Imparato	Retrospective	155	Not stated	Not defined	90.3%	Not reported	None reported
Shull	Retrospective	81	(24-60)	Grade 0-1	82%	Apex 4% Anterior 12% Posterior 1%	4 (5%)
Pasley	Retrospective	144	35 (6-83)	Asymptomatic and above hymen	85.4%	Apex 5.6% Anterior 7.6% Posterior 1.4%	2 (1.3%)
Benson	RCT SSLS vs ASC	42	30 (12-66)	Vaginal walls above hymen or apical descent less than 50% length[#]	67%	Apex 12% Anterior 28.5% Posterior 2.3%	14 (37%)
Paraiso	Retrospective	243	76. (1-190)	Grade 0 or asymptomatic Grade 1	79.7%	Apex 4.9% Anterior 15.9% Posterior 4.9%	11 (4.5%)
Penalver	Retrospective	160	40 (18-78)	'Any symptomatic descent'	85%	Apex 6% Anterior 6% Posterior 2.5%	11 (6.8%)
Colombo	Retrospective	62	83 (48-108)	Grade 0-1	74%	Apex 8% Anterior 14% Posterior 3%	0 (0%)
Meschia	Retrospective	91	43 (12-86)	Grade 0-1	85%	Apex 4% Anterior 13% Posterior 9%	None reported

First Author (year)	Study Design	n	Mean Follow-up Mo. (range)	Definition of Anatomic Success*	Anatomic Success	Anatomic Recurrence by Segment	Reoperation for POP
Sze	Retrospective	75	24 (3-72)	Above hymen	71%	Anterior 21% Other 8%	7 (12.9%)
Lantzsch	Retrospective	123	58 (6-108)	Not defined	87%	Apex 3.5% Anterior 8% Posterior 1.6%	2 (1.6%)
Lovatsis	Retrospective	293	(12-30)	At or beyond the introitus	97%	Apex 3% Anterior NR Posterior NR	3%
Cruikshank	Prospective cohort	695	43 (6-60)	Reoperation for recurrence	89.4%	Apex 5.1%	105 (15%)
Niemenen	Retrospective	138	24	POP-Q Stage 2 or greater	78.7%	Apex 4.9% Anterior 11.5% Posterior NR	NR
Maher	RCT SSLS vs. ASC	48	22 (6-58)	Grade 0-1	69%	Apex 19% Anterior 14% Posterior 7%	3 (6.3%)
Hefni	Prospective	305	57 (24-84)	Vaginal vault at least 6 cm distal to hymen	96%	Apex 4% Anterior 13% Posterior 0%	NR
Toglia	Retrospective	64	26.5 (1-72)	Apex above introitus and no reoperation	78%	Apex 9% Anterior 17% Posterior 0%	2 (3%)
Aigmueller	Prospective	55	84 (24-180)	Above the hymen	64%	Apex 7% Anterior 29% Posterior 5%	5 (9%)
Chou	Retrospective	76	36 (12-60)	Grade 0	91%	Apex 5.3% Anterior 3.7% Posterior NR	4 (5.3%)
Barber	RCT	186	24	Composite	60%		

In summary, SSLF has reoperation rates which range from 1.3% to 37%, transfusion rates of about 2%, and transient buttock pain in 3%.

Table 10. Single Incision TVM Kits

Author (year)	Number Total/ (F/U)	Device # in each	Study Type/ F/U	Anatomic Success	Subj	Exposure Rate	Comments
Uphold							
Vu (2012)	115 (110)	Uphold	Retro – 12.1 m (0.4-30.9 m)	Defined as C ≥ 0 0% in hysteropexy 0% in cuff 4.2% with hyst	93% by SSQ	2.6%	Prior Hyst: 21% Concomitant Hyst: 22% Hysteropexy: 48%
Rivaux (2012)	59	Uphold	Longitudinal – 12 m	Defined as Ba and C < 1: 93%		3.5%	In French Mainly Hysteropexy
Letouzey (2015)	115	Uphold	Longitudinal – 23 m (min of 12 m)	93%			8% denovo dyspareunia reop for mesh complications including pain and erosion- 3.4%
Elevate-AA only							
Moore (2012)	60	Elevate-AA	Retro – 13.4 m	91.7% (≤ Stage 1)		0%	Prior Hyst: 73% Hysteropexy: 27%

Author (year)	Number Total/ (F/U)	Device # in each	Study Type/ F/U	Anatomic Success	Subj	Exposure Rate	Comments
Stanford (2012)	142 (112)	Elevate-AA	Prospective – 12 month	Defined as ≤ Stage 1: 87.7% anterior 96% apical		2%	Prior Hyst: 44% Concomitant Hyst: 20% Hysteropexy: 36%
Stanford (2015)	142	Elevate-AA	Prospective – 24 month	Defined as ≤ Stage 1: 70.8%-89.1% anterior 93.8%-100% apical		Prior Hyst-4.9% Concomitant Hyst-13.8% Hysteropexy -2%	Prior Hyst: 44% Concomitant hyst: 20% Hysteropexy: 36% Large # data points missing at 24 months
Wong (2014)	91 Elevate 138 Perigee	Perigee Elevate-AA	Longitudinal – 12 month	Defined as ≤ Stage 1: 54%	76%		Prior Hyst: 52% Concomitant Hyst: 8% Hysteropexy: 40% This is the only paper with significant failure rate with elevate but used -2 and -3 as success.
Rapp (2014)	42 (40)	Elevate-AA	Retro – 24 month	Defined as > -1: 90%	93%	5%	Anatomic failure: 2-ant 2-apical
Lo (2015)	65	Elevate-AA	Prospective – 12 month	Defined as Stage 1 or less: 96.9%	93.8%	0%	All Stage III and IV POP Prior Hyst: 11/65 (17%) Concomitant Hyst: 54/65 (83%)
Rogowski (2015)	114	Prolift (52) Elevate-AA (62)	Retro – 18 month	Defined as anterior POP Stage 0 or 1 (less than -1), no retreatment: 90% Beyond Hymen: 93.5%	Bulge	7.7% prolift 0% elevate	Prior Hyst, Concomitant Hyst, and Hysteropexy not discussed
Long CY (2015)	141	Perigee (91) Elevate-AA (50)	Retro – 12 month	Defined as most point < Stage 2 (+1): 94%		11% Perigee 2% Elevate	Prior Hyst: 10/50 (20%) Concomitant Hyst: 16/50 (32%) Hysteropexy: 24/50 (48%)
Marschke (2015)	109 (70)	Elevate-AA	Retro – 13 month	Defined as Stage 0 and 1: 95.7%		5.7%	All Prior Hyst Stage III and IV
Elevate: AA, Post, Both							
Azais (2012)	70	Elevate AA- 20 Post-16 Both-34	Prospective – 12 month	Defined as leading edge -2: 68.7%		4.5%	Prior Hyst: 15.7% Concomitant Hyst: 5.7% Hysteropexy: 78.6% 4 cases of de novo dyspareunia Unable to assess different procedures for success
Lukban (2012)	139 (126)	Post Elevate	Prospective – 12 month	Defined as ≤ Stage 1: 93.5% post 89.2% apical	Very or extremely satisfied: 81%	6.5%	Prior Hyst: 57.6% Concomitant Hyst: 14.4% Hysteropexy: 22%
Su (2014)	100	Both Elevate-AA and Post Elevate in all patients	Cohort – 12 month with NT arm	Defined as ≤ Stage 1: 98% ant 99% apical 100% post		3%	Prior Hyst: 17% Concomitant Hyst: 75% Hysteropexy: 7%

Author (year)	Number Total/ (F/U)	Device # in each	Study Type/ F/U	Anatomic Success	Subj	Exposure Rate	Comments
Huang (2015)	210 (200)	Elevate AA- 31 (15.5%) Post-4 (2%) Both-165 (82.5%)	Retrospective – 27 month	Defined as Stage 1 or 2: 94%	UDI-6, IIQ, POP-Q – all improved	1.8%	Prior Hyst: 35/200 (17.5%) Concomitant Hyst: 110/200 (67.5%) Hysteropexy: 53/200 (32.5%) Stage 3 and 4 5 repeat surgery

APPENDIX B. PPAR SECONDARY AIM

Study Aims – Patient-Perspective in AE Reporting (PPAR)

Adverse event (AE) and harms assessment in clinical trials is critical to allow patients and health care providers weigh the potential benefits, harms, and invasiveness of different treatment options. Although many trials use robust methodology to detect potential treatment benefits, there has been less focus on the assessment of complications and their association with quality of life (AEs). There are several challenges to AE reporting and measurement, including a lack of understanding of the patient perspective. In 2008, the Agency for Healthcare Research and Quality (AHRQ) emphasized that knowledge about AEs and adverse symptoms from the patient perspective is a key component required to capture all important harms that could influence patient decision-making.

The overarching aim of this supplementary proposal is to improve our understanding of the patient perspective about complications and harms and their role in patient decision-making outcomes. Improving our understanding will inform the development of a shared model for AE reporting in PFD treatments that includes both the patient and clinician perspective, since both are meaningful. The aims of PPAR include comparing patient versus surgeon rankings of complication grade, outcome, expectedness, and seriousness, to estimate the association between patient rankings of AEs with decision-making and quality of life outcomes, and to determine if their perspective about AEs changes over time.

Significance: The proposed study is of high clinical significance because the measurement and monitoring of surgical adverse events is currently imprecise and of uncertain validity. Capturing the patient perspective is paramount to help ensure that all aspects of AEs/symptoms that may influence patient treatment decision-making are captured. The data from this study will be used to provide insight into which AEs/symptoms are: 1) relevant to patients and 2) associated with treatment and decision-making outcomes and quality of life (result in harm). This information will improve the comprehensiveness of our counseling about the risks and benefits of the three surgical treatments included in ASPIRe and is a first step to improving the process for collection, reliability, and validity of AE information collected in studies of pelvic floor surgical treatments.

PPAR Study Aims

Aim 1: To compare patient vs. routine rankings* of AE/adverse symptom grade.

This aim will provide information about the relevance and severity of AEs/symptoms from the patient perspective via a ranking process and will also compare patient rankings with our current routine ranking process.

We hypothesize that the patient ranking and routine ranking processes will result in differences in perceived severity (grade).

Aim 2: To estimate the association between patient rankings of AE/symptom grade and impact to Decision Regret and Decision Satisfaction in ASPIRe.

We hypothesize that symptoms and events graded by patients as severe will be associated with higher Decision Regret and lower Decision Satisfaction scores compared to less severe events. This will provide data to inform which events are associated with harm (negative impact on decision-making and quality of life outcomes).

Aim 3: To estimate the association between AEs/symptoms and quality of life and patient global impression outcomes (SF-12 and PGI-I).

We hypothesize that symptoms and events graded by patients as more severe will be associated with decreased quality of life and global impression scores. This also provides data to inform which events are associated with harm.

Aim 4: To determine if patient perspective about AEs/symptoms changes over time.

We hypothesize that the patient perspective about adverse symptom and event attributes such as grade and impact on decision-making and quality of life outcomes will change over time and ultimately plateau. This will potentially provide information about the most relevant time points at which to measure specific events.

Aim 5: To compare AE/symptom severity ranking between patient rankings and the Pelvic Floor Complication Scale.

We hypothesize that AE ranking based on patient perspective compared to the PFCS will be different. Because the PFCS was developed by the PFDN, it is important to provide validity data from the patient perspective.

Aim 6: To begin to develop a shared model of AE/symptom reporting, incorporating both patient and clinician input.

3. BACKGROUND AND SCIENTIFIC RATIONALE

3.1. Definitions of adverse events:

Complications and event reporting after treatment is an important component in the assessment and comparison of new and existing interventions as well as in clinical trials and comparative effectiveness studies. There are at least two critical reasons why good quality data about events and complications after surgical treatment are needed. First and foremost, a comprehensive understanding of complications associated with treatments is important for patient treatment decision-making and to allow balanced counseling of options between a health care provider and the patient. Second, purchasers and payers have an increasing interest in surgical complications and the quality of surgical care, as complications can be very costly. [1] Despite these strong reasons, the measurement and monitoring of complications is often imprecise and of uncertain validity, [2] taking a back seat to the measurement of efficacy and methodology. Weak measures and inconsistent methodology ultimately result in weak data.

The terms “harm”, “adverse events”, and “complications” are often used to represent the same concept, however can have different definitions depending on source (Table 11). A common medical definition of *complication* is “a secondary disease or condition that develops in

the course of a primary disease or condition and arises either as a result of it or from independent causes". *Adverse event* is defined by the Food and Drug Administration (FDA) as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related". The Office of Human Research Protections defines *adverse event* as "Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research." These definitions are primarily used for regulatory purposes, and do not directly consider the patient's perspective or experience of the events. The Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE) has its own definition, with a grading scale that considers whether an AE resulted in limitations in instrumental activities of daily living. The CTCAE was developed to critically and systematically monitor AEs linked to oncology research.

Perhaps a more patient-centered definition has been offered by the Canadian Disclosure Guidelines [3]: *harm* is "an outcome that negatively affects a patient's health and/or quality of life"; an *adverse event* is "an event which results in unintended harm to the patient, and is related to the care and/or services provided to the patient, rather than to the patient's underlying medical conditions." This last definition offers a more useful definition that considers the patient perspective [4]; however, little work has been done to understand which postoperative events may result in harm to our patients.

Table 11. Definitions of Some Postoperative Events

Term	Source	Definition
Complication		Secondary disease/condition that develops in the course of a primary disease/condition and arises either as a result of it or from independent causes
Adverse Event	FDA	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
Adverse Event	OHRP	Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the participant's participation in the research
Adverse Event	CTCAE	Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.
Adverse Event	Canadian Disclosure Guidelines	An event which results in unintended *harm* to the patient, and is related to the care and/or services provided to the patient, rather than to the patient's underlying medical conditions
Harm	Canadian Disclosure Guidelines	An outcome that negatively affects a patient's health and/or quality of life

3.2. Limitations in existing mechanisms to capture complications/AEs:

Collecting data about complications and "adverse events" in clinical trials is challenging for many reasons:

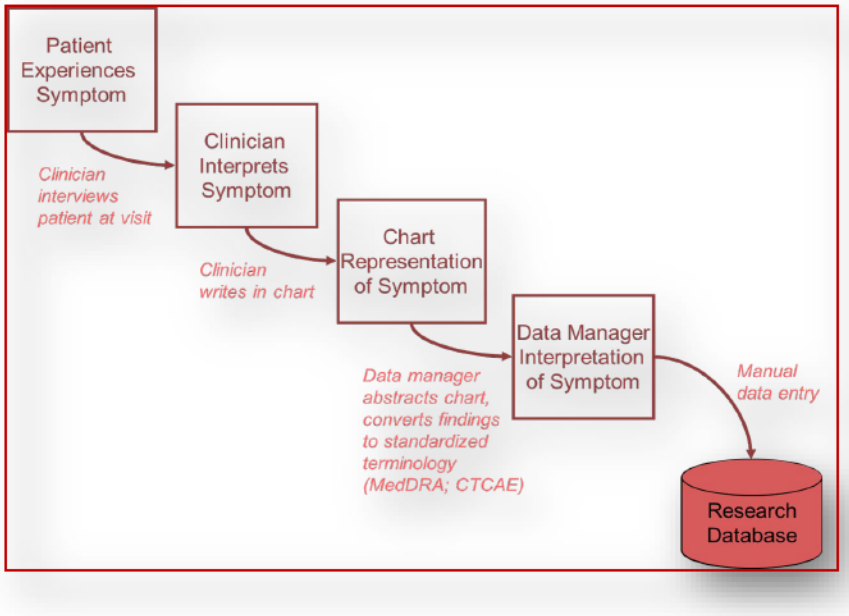
1. There is no specified methodology to elicit symptomatic AEs from participants.
2. There is no standard or required training of investigators or research staff for AE collection.
3. The workflow and reporting mechanisms vary between and within study sites.
4. There is lack of obtaining the patient perspective in standard AE reporting processes.

Several coding systems have been developed primarily to standardize AE collection to address regulatory requirements including the CTCAE and the Medical Dictionary for Regulatory Activities Overview (MedDRA). Both of these systems rely on medical terminology and to some extent, subjective input from the clinician or researcher. CTCAE was originally developed for oncology research and may not include guidance for pertinent events that may be common after pelvic floor treatments. MedDRA provides recommended terminology and classification for AE reporting, but similar to CTCAE does not incorporate patient perspective.

Additional discussion about the CTCAE is warranted because currently it serves as a guide for AE reporting within PFDN trials. The CTCAE is the standard approach to AE reporting in cancer trials and is maintained by the National Cancer Institute (NCI). The CTCAE includes about 790 items, each representing a discrete event which is graded for severity on a 5-point scale based on clinical criteria. There are three general categories of AEs in the CTCAE and MedDRA: 1) laboratory-based events (e.g. neutropenia), 2) observable/measureable events (e.g. vomiting), and 3) symptomatic AEs (e.g. nausea). For this third category, symptomatic AEs (or "adverse symptoms"), research has shown that this method of clinician reporting lacks reliability, [5] and that clinicians under-report the incidence and severity of symptoms compared to patients' direct reports, [6] and that patient reports better reflect underlying health status than clinician reports. [7, 8]

Currently, the workflow of symptomatic AE reporting in many trials, including PFDN trials, involves a series of data transfers between the patient and multiple professional staff members (see Figure 1). Information may be lost or misinterpreted at every step, particularly considering the limitations of existing mechanisms already discussed above. Each step is one additional step removed from the patient's perspective.

Figure 1. Common model for adverse event and symptom reporting.
Adapted from Basch et al. J Natl Cancer Inst (2014) [9]



Other complication grading scales were developed from the clinician/surgeon perspective including the Clavien-Dindo and Pelvic Floor Complication Scale. [10-12] The Clavien-Dindo scale is primarily oriented to general surgery procedures, [11] whereas the Pelvic

Floor Complication Scale (PFCS) was developed to try and capture the magnitude and consequence of complications specifically for women undergoing pelvic reconstructive surgery. [10] These scales were developed primarily based on the opinion of surgeons regarding the significance and severity of each complication without patient input. It has been well established that for many outcomes the clinician and the patient perspective can differ significantly. Surgeons often weigh the severity of surgical complications based on the need to return to the operating room or whether it is life-threatening. However, this likely does not capture complications that patients may consider important or severe. For example, although the PFCS was developed to enhance the Clavien-Dindo scale for pelvic reconstructive procedures, both scales showed limited overall predictive value when assessing associations between complications and bother and quality of life measures at 3 months. This supports that there is likely discordance between surgeon and patient definitions of harms associated with complications and highlights the importance of including the patient's subjective experience in AE reporting.

3.3. Work in other fields towards a patient-centered approach to adverse event reporting:

NCI recognized the limitations of the CTCAE in capturing symptomatic AEs and has worked to significantly expand the scope of the CTCAE through direct integration of the patient perspective starting in 2008. [9] A consortium was established with the goal of developing a standardized measurement system that can accurately and reliably detect events from the patient perspective and the system is called the PRO-CTCAE. The PRO-CTCAE was developed with the capacity for investigators to select relevant items to generate tailored patient surveys and to schedule and electronically administer those surveys to participants via web or automated telephone IVR. 78 items from the CTCAE were identified as being amenable to self-reporting by adults with cancer and these are the AEs that are currently in the PRO-CTCAE version 1.0 library. NCI has made significant strides in the development of the PRO-CTCAE, although it is currently in testing format. Furthermore, the included adverse symptoms are most relevant to cancer trials and the majority are not relevant to pelvic floor disorders.

3.4. Need for PPAR:

Currently, AE symptom reporting is burdensome and time consuming for research staff and investigators. It is also inefficient especially when it is unclear which events are relevant to patients. The measurement and monitoring of AEs is often imprecise and of uncertain validity, but it is a fundamental piece of treatment evaluation. Even with using the CTCAE as a guide, reporting can be variable in terms of "grade" and "expectedness" between sites as well as within the same type of AE (e.g. findings from the SUPeR AE Adjudication Task Force). The SUPeR AE Adjudication Task Force was developed to help improve the consistency and reliability of AE reporting between clinical sites for the SUPeR trial, however we are still missing the patient perspective. Addressing this gap will help inform the relevance and impact of AEs from the patient perspective and guide and streamline future reporting for complications specific to pelvic reconstructive procedures.

In summary, gaining information about the patient perspective on all aspects of a treatment option is an important piece of information that is necessary for patient decision making, yet remains missing from our current knowledge about AEs. Currently there is minimal information regarding which complications are considered to be "serious" or relevant by patients, and which complications result in *harm*. Additionally, the duration of follow-up and ideal timing of measurement for individual events will likely vary according to their natural history and patient impact but this has not been well explored. These data can further contribute to understanding the association between specific complications and whether they result in harm

(negative impact on quality of life), and patient perceptions about surgical and decision-making outcomes. This will provide a more comprehensive assessment of risks and benefits for pelvic reconstructive procedures. This understanding is particularly important for the ASPIRe trial, because each of the three interventions likely has a different risk-benefit profile (e.g. potential mesh complications in 2 of the 3 arms).

4. STUDY OBJECTIVES AND PURPOSE OF PPAR

Aim 1: To compare patient vs. routine rankings* of AE/symptom grade.

This aim will provide information about the relevance and severity of adverse symptoms and events from the patient perspective via a ranking process and will also compare patient rankings with the routine ranking process.

We hypothesize that the patient ranking versus routine ranking processes will result in differences in perceived severity (grade) and impact.

* "Routine ranking" is defined as the usual PFDN process for grading AEs, which typically incorporates research staff and investigator/surgeon input.

Aim 2: To estimate the association between patient rankings of AE/symptom grade and impact to Decision Regret and Decision Satisfaction in ASPIRe.

We hypothesize that symptoms and events graded by patients as severe will be associated with higher Decision Regret and lower Decision Satisfaction scores compared to less severe events. This assessment will provide data to inform which events are associated with harm (negative impact on decision-making and quality of life outcomes).

Aim 3: To estimate the association between AEs/symptoms and quality of life and patient global impression outcomes (SF-12 and PGI-I).

We hypothesize that symptoms and events graded by patients as more severe will be associated with decreased quality of life and global impression scores. This also provides data to inform which events are associated with harm.

Aim 4: To determine if patient perspective about AEs/symptoms changes over time.

We hypothesize that the patient perspective about adverse symptom and events qualities such as grade and impact on decision-making and quality of life outcomes will change over time and ultimately plateau. This will potentially provide information about the most relevant time points at which to measure specific events.

Aim 5: To compare AE/symptom severity ranking between patient rankings and the Pelvic Floor Complication Scale.

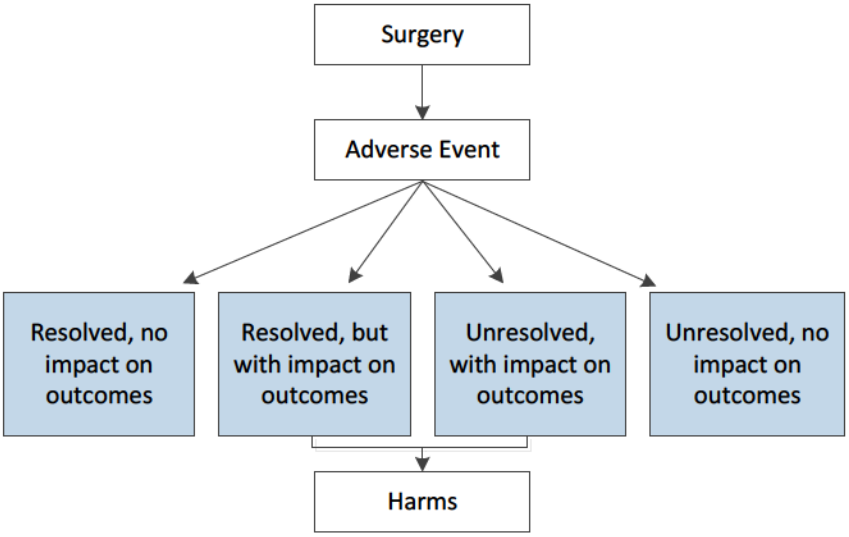
We hypothesize that AE/symptom ranking based on patient perspective compared to the PFCS will be different. Because the PFCS was developed by the PFDN, it is important to provide validity data from the patient perspective.

Aim 6: To begin to develop a shared model of AE/symptom reporting, incorporating both patient and clinician input.

5. STUDY DESIGN

5.1. Description of study design:

PPAR is designed to fill several gaps regarding the patient perspective and to determine which postoperative events are associated with a negative impact on decision-making and quality of life outcomes, or in other words resulting in harm. This is outlined in Figure 1.



PPAR is designed to provide supplementary information to the ASPIRe core study. ASPIRe is a three-armed surgical trial comparing transvaginal mesh (Uphold LITE) vs. sacral-colpopexy, and native tissue repair vs. sacral-colpopexy and transvaginal mesh for post-hysterectomy vaginal vault prolapse. In the ASPIRe protocol, AEs will be assessed longitudinally through the 5 year trial duration and routinely at 6 month intervals.

Standard AE Capture Process

ASPIRe AEs are captured by research staff either by phone or in-person follow-up visits. Collection includes both active (select AEs that patients are questioned about specifically) and passive capture (rely on patient reporting to staff that AE occurred). AEs are then logged into an AE log form, for which there are 7 fields that are required (Table 12). The routine process is for research staff to collect any additional documentation of the event, and then to complete the AE Log form and the 7 additional fields with input from each site's investigators. This process is primarily designed to meet several regulatory guidelines on AE reporting. This process will be referred to as "Usual Ranking" of AEs.

Table 12. Standard AE Descriptors Collected in Usual Ranking (AE Log Form)

AE Descriptor:	Response Options:
Grade	Mild, moderate, severe, life-threatening, death
Attribution: Relation to Study Intervention	Unrelated, unlikely, possible, probable, definite
Action	None, sought medical attention, additional surgery, hospitalization, other, unknown
Outcome	Resolved, resolved w/sequelae, unresolved, fatal, unknown
Expected AE?	Yes or no
Serious AE	Yes or no
Continuing?	Yes or no

PPAR AE Capture Process

For PPAR, we will obtain patient input on pre-selected adverse events and symptoms through "active capture". The team recognized the main limitation of the active capture approach is that there may be AEs that patients consider important that may not be included in PPAR. However, we believe that for this supplementary study, active capture would be the most feasible approach to collecting data that is reliable. We believe this data will be meaningful and will allow us to begin the process of assessing the impact of AEs from the patient perspective.

We anticipate there will be adverse events that are discrete events (e.g. urinary tract infection) and others that are adverse symptoms (e.g. dyspareunia). For discrete *adverse events*, we will ask patients to grade the severity and rate the impact of the event. For *adverse symptoms*, patients will be asked to provide information about severity, frequency, and impact of the adverse symptom. This participant assessment will be referred to as "Patient Ranking" of AEs and is presented in Table 13.

Table 13. PPAR Adverse Event and Symptom Attributes

AE Descriptor:	Patient Question*	Response Options:
1. Adverse events		
Severity at its worse	How would you grade or rank this event?	Mild, moderate, severe, life-threatening
Impact	How much did the event/ symptom interfere with your usual or daily activities?	Not at all / A little bit / Somewhat / Quite a bit / Very much
2. Adverse symptoms		
Frequency	How often did you experience the symptom	Rarely, occasionally, frequently, almost constantly
Severity at worst	What was the severity level of the symptom at its worst?	Mild, moderate, severe, very severe
Impact	How much did the event/ symptom interfere with your usual or daily activities?	Not at all / A little bit / Somewhat / Quite a bit / Very much

5.2. Rationale for AEs/symptoms included in PPAR:

For the standard AE capture process in ASPIRe, AE capture will follow these guidelines:

- 0-6 weeks postop: All AEs grade 2 (moderate) or higher are captured.
- 6 weeks to 6 months: All AEs and SAEs involving death, hospitalization or ER visit, and grade 2 or higher at least possibly related to surgery in the opinion of the investigator are captured.
- After 6 months: Deaths, AEs and SAEs grade 2 or higher that are at least possibly related to pelvis or surgery in the opinion of the investigator are captured.

There are several AEs that will be actively captured as part of ASPIRe. For PPAR, a list of pre-selected adverse events and symptoms will undergo the Patient Ranking process, which will include many of those already being actively captured in ASPIRe. A list of adverse events and symptoms for PPAR is in Appendix B-3. The highlighted events and symptoms are those that are already planned for active capture in ASPIRe. There are 11 adverse symptoms and 7 adverse events to be captured in PPAR.

Selection of AEs to Capture in PPAR

The AEs and symptoms selected for PPAR are based on review of the Pelvic Floor Complications Scale (Appendix B-1), the PRO-CTCAE library (Appendix B-2), findings and content informing the PASEo protocol, and the protocol team's input and consensus.

There was significant discussion regarding whether or not urinary incontinence (stress (SUI) and urgency (UUI) should be captured as AEs/symptoms. In ASPIRe, the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ) will be administered which capture presence and bother of these symptoms as patient-reported outcomes. In an effort to minimize duplicate capture, there have been previous suggestions (SUPeR AE Adjudication Committee) to rely solely on the PFDI and PFIQ to determine whether or not a patient may be experiencing these symptoms and that these could substitute for the usual AE capture process for these symptoms. Therefore, the team, along with the PFDN Steering Committee members, discussed at length: (1) whether these should be considered AEs/Symptoms versus just as outcomes and (2) if SUI and UUI should be considered as potential adverse symptoms and how to best capture these for PPAR.

After discussion with the Steering Committee, the team determined that it was still important to consider SUI and UUI as potential adverse symptoms since they may be perceived as such by patients, and because neither SUI nor UUI are part of the *primary outcome* in ASPIRe.

We then explored how to best capture SUI and UUI for PPAR. The DCC explored whether there could be a feasible approach to utilizing the PFDI responses as a substitute for capture of SUI and UUI as AEs/symptoms that would help decrease the workload for coordinators, but still preserve the reliability and integrity of the data captured. Unfortunately, there was not a simple solution that would prospectively allow coordinators to be alerted to PFDI responses and allow them to track these events in real time for PPAR. Therefore, the decision was made that SUI and UUI would be included in the PPAR inventory and the clinical and patient perspective would be captured in the usual process as described below for all other AEs/symptoms for PPAR.

One potential advantage of defaulting to this approach is that we can validate whether or not the PFDI can be used as a substitute in future trials (such as prolapse trials) to capture SUI and UUI as AE/symptoms if the information obtained through both approaches is similar.

6. SELECTION OF PARTICIPANTS

Inclusion and Exclusion Criteria: All women who participate in ASPIRe will be included in this supplementary study, with the same inclusion and exclusion criteria. As with the primary ASPIRe study, only randomized and treated participants will be included in the analysis.

7. DESCRIPTION OF STUDY INTERVENTIONS

The PPAR AE Log form will be similar to the Standard AE Log Form used for the usual ranking process to capture the PPAR attributes (grade/severity at its worst, impact, frequency). The 6-week and 6-60 month postoperative ASPIRe visit forms will include the PPAR inventory items under "Subject Reported Complications Table" to streamline capture from the coordinator standpoint. PPAR items on these forms will be highlighted using a mechanism such as an *asterisk to alert the coordinator that additional PPAR forms will be required for those AEs/symptoms.

We will collect PPAR data at the time points outlined in Table 14.

Table 14. Collection of Patient-Perspective Information for AEs

Time point	Rationale
Initial identification of AE	Provides patient's initial perspective *This gets updated at each interaction such that the "most severe" reporting by the patient gets recorded.
12 months postop	Provides information about whether her perspective changed over time
3 years postop (or final visit)	Provides her final perspective about the AE at the primary endpoint of the ASPIRe trial

When a PPAR AE/symptom is identified, the research staff will capture the PPAR AE/symptom attributes with the patient. The research staff will complete the usual process as needed to complete the Standard AE Log Form as well as the PPAR AE log Form. The investigators will be masked to the patient reporting and the patients will be masked to the investigator reporting. The attributes will be captured in an ongoing fashion such that the highest severity reported by the participant will be recorded on the PPAR AE log. Her perspective will be reassessed at 12 months and 3 years postoperative. Whether or not (and when) the AE/symptom has resolved will be determined based on the Standard ASPIRe AE log form by the field "Event End Date".

We did consider capturing PPAR information at the time the AE/symptom resolves. The team decided that it would be challenging to collect the patient perspective at the exact time point that the participant considered the event or symptom resolved, as this would require fairly intense tracking. Therefore, tracking will not be performed to specifically define when an event or symptom resolved. However, again, an estimate of if and when the event/symptom resolved will be captured on the ASPIRe AE log form and will be used in PPAR analyses to determine whether the participant perspective was collected before or after resolution. If over time the AE worsens, then the PPAR attributes will be collected again to provide information regarding if her perspective has changed.

Logistically, the decision-making and quality of life scales are to be administered prior to obtaining PPAR information to minimize any bias that may occur with completing PPAR associated forms.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1. Sample size:

There is very little information regarding patient perspective for AEs.

Table 15 presents information regarding AEs in previous PFDN trials that have included pelvic organ prolapse repair, specifically apical suspension procedures.

Table 15. AEs in Prior PFDN Trials Including Surgical Treatment for Apical Prolapse

PFDN Trial	Total Number of Patients in Trial	Number of SAEs	Number of AEs Possibly Related to Study	Unexpected AEs	Total AEs
SUPeR	184	18 AEs	~60% of total AEs		300 AEs
OPUS	337	52*	219 AEs	31*	302 AEs

PFDN Trial	Total Number of Patients in Trial	Number of SAEs	Number of AEs Possibly Related to Study	Unexpected AEs	Total AEs
OPTIMAL	374	84 SAEs (but only 14 likely related to study)	160 patients		? 244 patients
ASPIRe	363				

*Includes events likely unrelated to study (e.g. colon cancer, knee fracture, goiter)

An analysis of the SUPeR data available at the time of protocol development indicated that approximately 300 AEs had been reported, with slightly more than 60% having a relationship of possibly related or greater to the intervention. Approximately 50% of women had reached the 1-year follow-up for SUPeR at that time. Based on this information, we estimated that 400 AEs would be identified for ASPIRe that would be possibly related to the study, including all grades. Assuming that the distribution of severity is comparable to that found in the SUPeR trial, this study is powered to provide an interval estimated for the agreement between clinician grading of +/- 0.11. That is, if the study estimate of Kappa measuring the agreement is 0.5, we will be 95% confident that the true agreement is in the range of 0.39 to 0.61.

8.2. Statistical methods:

Aim 1: To compare patient vs. routine rankings of AE/symptom grade.

We will compare the proportions of AE rankings based on grade using Chi-square between patient and usual rankings. We will also determine the inter-rater agreement between the two groups by estimating the Cohen's Kappa coefficient. In addition to these tests, which provide an overall assessment of whether or not the ratings between clinicians and patients agree or disagree, we will also use extensions of generalized linear models that are appropriate for the ordinal nature of these outcomes and the paired structure of the patient/clinician ratings to evaluate how patients and clinicians disagree should the initial tests suggest differences. Specifically, we will explore classes of events for which the rankings of patients are consistently lower or higher than those of the clinicians.

Aim 2: To estimate the association between patient rankings of AE/symptom grade to Decision Regret and Decision Satisfaction in ASPIRe.

We will estimate the association between patient determined grade and impact of AEs and Decision Regret and Decision Satisfaction scores using linear model approaches. Mean scores for these scales will be compared between women who experienced serious AEs and different grades and impact of AEs. These scores will be compared at the 12 month and 3 year time points.

Aim 3: To estimate the association between AEs/symptoms and patient and quality of life and patient global impression outcomes (SF-12 and PGI-I).

We will utilize a combination graphical summaries and linear model-based approaches to compare the mean SF-12 and PGI-I scores between women who experienced severe AEs/symptoms and to compare these means across women who exhibit the different AE/symptom grades. These scores will be compared at the 12 month and 3 year time points.

Aim 4: To determine if patient perspective about AEs/symptoms changes over time.

We will determine the intra-observer agreement for patient rankings of AE/symptom grade and impact over time using weighted Kappa measures. We will also explore whether the impact of specific events plateaus over time, taking into account her perception of if and when the AE/symptom resolved.

Aim 5: To compare AE/symptom severity ranking between patient rankings and the Pelvic Floor Complication Scale.

We will develop a list of AEs, using the previously published Pelvic Floor Complication Scale (PFCS) as a guide. Appendix B-1 presents AEs ranked by severity based on physician rankings for the PFCS. We will develop a similar ranking list based on our patient rankings by AE grade and qualitatively compare and describe differences and similarities between these two ranking lists.

Aim 6: To begin to develop a shared model of AE/symptom reporting, incorporating both patient and clinician input.

Clinician reporting of adverse events is highly associated with clinical endpoints of death and hospitalization in cancer trials, as their impressions are based on professional training and experience. Patient reporting is more highly associated with measures of day to day health status and better reflects the short and or long-term impact of AEs. Therefore, these are complementary perspectives and a shared reporting model is likely ideal. We will work to develop a shared reporting model.

9. POTENTIAL LIMITATIONS OF PPAR

As noted above, one limitation to the “active capture” approach in PPAR is that we may miss some events or symptoms that patients consider relevant; however, PPAR serves as an early step to obtaining the patient perspective about AEs/symptoms. We anticipate that the proposed approach will be feasible and importantly, will provide meaningful and reliable data.

10. POTENTIAL STRENGTHS OF PPAR

A primary strength of PPAR is that potential harm will be assessed in several ways including: (1) measurement of impact/interference of the AE/symptom; (2) impact on decision-making outcomes; and (3) impact on quality of life and global impression outcomes. Another advantage of capturing the patient perspective at the time of AE reporting is that we can capture her experience in real time, instead of relying on retrospective recall or hypothetical scenarios. Although other studies have focused on complications in the immediate perioperative period, this study will also provide some insight into the patient’s experience of AEs after discharge and for AEs that are experienced further out from the time of the index surgery. We will determine which events are associated with harm (short-term and/or long-term impact on decision-making and quality of life). Also, capturing the patient perspective using our usual ranking form will be complementary to ASPIRe’s exploratory aim of developing a global composite outcome. Finally, the results of PPAR will help guide and streamline the Network’s AE reporting, making it more patient-centered and relevant. It will either confirm that our current process is relevant, or more likely, will help to improve on our current process, particularly as we work to develop a shared model of reporting that includes both clinician and patient perspectives. Although we recognize that PPAR is only a start at incorporating the patient perspective and cannot be comprehensive, ultimately PPAR will help to present a more balanced representation of patient experience after undergoing one of the three procedures in ASPIRe.

REFERENCES

1. Dimick J, Chen S, Taheri P, et al. Hospital costs associated with surgical complications: a report from the Private-sector National Surgical Quality Improvement Program. J Am Coll Surg. 2004;199:531-537.
2. Bruce J, Russel EM, Mollison J, Krukowski ZH. The measurement and monitoring of surgical adverse events. Health Technol Assess 2001;(5)22:1-194.
3. Disclosure Working Group. Canadian Disclosure Guidelines. Edmonton, Alberta: Canadian Patient Safety Institute; 2008.
4. Parry G, Cline A, Goldmannd. Deciphering harm measurement. JAMA 2012; 307(20):2155-2156.
5. Atkinson TM, Li Y, Coffey CW, et al. Reliability of adverse symptom event reporting by clinicians. Qual Life Res 2012;21:1159-64.
6. Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med 2010;362:865-9.
7. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. Lancet Oncol 2006;7:903-9.
8. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 2009;101:1624-32.
9. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106.
10. Gutman RE, Nygaard IE, YE W, et al. The pelvic floor complication scale: a new instrument for reconstructive pelvic surgery. American journal of obstetrics and gynecology 2013;208:81 e1-9.
11. Clavien PA, Barkun J, DE Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Annals of surgery 2009;250:187-96.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery 2004;240:205-13.

Appendix B-1. Pelvic Floor Complication Scale

Morbidity	Mean	SD
Intraoperative (before leaving operating room)		
OR1: Bowel injury with colostomy	8.2	0.7
OR2: Bowel injury with resection and primary repair	6.9	1.0
OR3: Bowel injury with primary repair (does not include serotomy)	5.9	1.4
OR4: Vascular injury that requires vascular surgeon	7.7	1.3
OR5: Ureteral injury that requires reanastomosis	7.0	0.9
OR6: Ureteral injury that requires stent	5.8	1.3
OR7: Ureteral injury that is resolved with removal of suture	4.4	1.6
OR8: Aspiration pneumonia	6.6	1.3
OR9: Transfusion	5.2	1.4
OR10: Estimated blood loss > 1000 mL	5.3	1.7
OR11: Urethral injury	5.8	1.3
OR12: Cystotomy that requires repair	4.7	1.2
OR13: Cystotomy that does not require repair	3.1	1.2
Immediately postoperation (after leaving operating room to discharge)		
IP1: Thromboembolic event (deep venous thrombosis/pulmonary embolism)	8.0	1.4
IP2: Small bowel obstruction	7.0	1.2
IP3: Ileus (reversal in diet advance)	3.8	1.2
IP4: Persistent nausea/vomiting > 24 hours (cause uncertain)	3.6	1.3
IP5: Postoperative fever that requires antibiotics (cause uncertain)	3.5	1.1
IP6: Postoperative fever that resolves without antibiotics	2.3	1.2
IP7: Myocardial infarction/congestive heart failure	8.6	1.0
IP8: Wound infection with fascial dehiscence	7.2	1.3
IP9: Wound infection/separation with suprafascial dehiscence	5.0	1.2
IP10: Wound infection/seroma/hematoma with no dehiscence (cellulitis resolved with antibiotics)	4.0	0.9
IP11: Fistula	7.5	1.3
IP12: Neuropathy that is persistent at time of discharge	6.0	1.6
IP13: Neuropathy that resolves before discharge	3.1	1.4
IP14: Urinary tract infection (bacteriuria, pyuria, treated with antibiotics)	3.3	1.1
IP15: Bleeding: reoperation required	7.3	1.1
IP16: Bleeding: transfusion required	5.3	1.3
IP17: Bleeding: observation only	3.4	1.4
IP18: Reoperation because of an unrecognized bladder injury	6.9	0.9
IP19: Reoperation because of an unrecognized ureteral injury	7.6	0.9
IP20: Reoperation because of an unrecognized bowel injury	8.3	1.0
IP21: Reoperation because of any other complication of original surgery	7.2	0.9
IP22: Pneumonia	5.7	1.4
IP23: Pulmonary edema	5.9	1.5
IP24: Mental status changes	6.0	1.6

Morbidity	Mean	SD
IP25: Pelvic abscess	6.6	1.5
IP26: Sepsis, disseminated intravascular coagulation	9.0	1.1
Delayed postoperative (after discharge)		
DP1: Thromboembolic event (deep venous thrombosis/pulmonary embolism)	8.2	1.4
DP2: Small bowel obstruction	7.1	1.0
DP3: Ileus (reversal in diet advance)	4.6	1.4
DP4: Persistent nausea/vomiting (cause uncertain)	4.3	1.5
DP5: Postoperative fever that requires antibiotics (cause uncertain)	4.1	1.1
DP6: Postoperative fever that resolves without antibiotics	2.7	1.2
DP7: Myocardial infarction/congestive heart failure	8.6	1.1
DP8: Wound infection with fascial dehiscence	7.5	1.2
DP9: Wound infection/separation with suprafascial dehiscence	5.3	1.3
DP10: Wound infection/seroma/hematoma – no dehiscence (cellulitis resolved with antibiotics)	4.3	1.2
DP11: Fistula	7.6	1.1
DP12: Urinary tract infection (bacteriuria, pyuria, treated with antibiotics)	3.5	1.1
DP13: Bleeding, reoperation required	7.5	1.2
DP14: Bleeding, transfusion required	5.6	1.5
DP15: Bleeding, observation only	3.6	1.5
DP16: Reoperation because of an unrecognized bladder injury	7.0	1.1
DP17: Reoperation because of an unrecognized ureteral injury	7.7	1.2
DP18: Reoperation because of an unrecognized bowel injury	8.5	1.1
DP19: Reoperation because of any other complication of original surgery	7.4	1.0
DP20: Pneumonia	5.7	1.5
DP21: Pulmonary edema	5.9	1.5
DP22: Mental status changes, dementia	6.0	1.7
DP23: Pelvic abscess	6.7	1.4
DP24: Sepsis, disseminated intravascular coagulation	9.0	1.1
DP25: Readmission secondary to a complication of original surgery	6.3	1.4
DP26: Graft erosion that requires surgical excision	6.0	1.4
DP27: Graft erosion trimmed in office	4.1	1.1
DP28: Graft erosion expectantly managed	3.3	1.2
DP29: Suture erosion	3.5	1.1
DP30: Urinary retention that requires surgical revision.	6.1	1.3
DP31: Prolonged urinary retention (> 4 wk) that requires catheterization	4.7	1.3
DP32: Transient urinary retention (< 4 wk)	3.2	1.3
DP33: Persistent neuropathy at (≥ 6 wk)	7.1	1.5
DP34: Granulation tissue	3.1	1.2

Robert E. Gutman, Ingrid E. Nygaard, Wen Ye, David D. Rahn, Matthew D. Barber, Halina M. Zyczynski, Leslie Rickey, Charles W. Nager, R. Edward Varner, Kimberly Kenton, Kimberly J. Dandreo, and Holly E. Richter. The Pelvic Floor Complication Scale: a new instrument for reconstructive pelvic surgery American Journal of Obstetrics and Gynecology, 2013-01-01, Volume 208, Issue 1, Pages 81.e1-81.e9

Appendix B-2. PRO-CTCAE Item Library

PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE™) ITEM LIBRARY (Version 1.0)

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	P
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Gynecologic/Urinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	P
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	PI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence /Amount

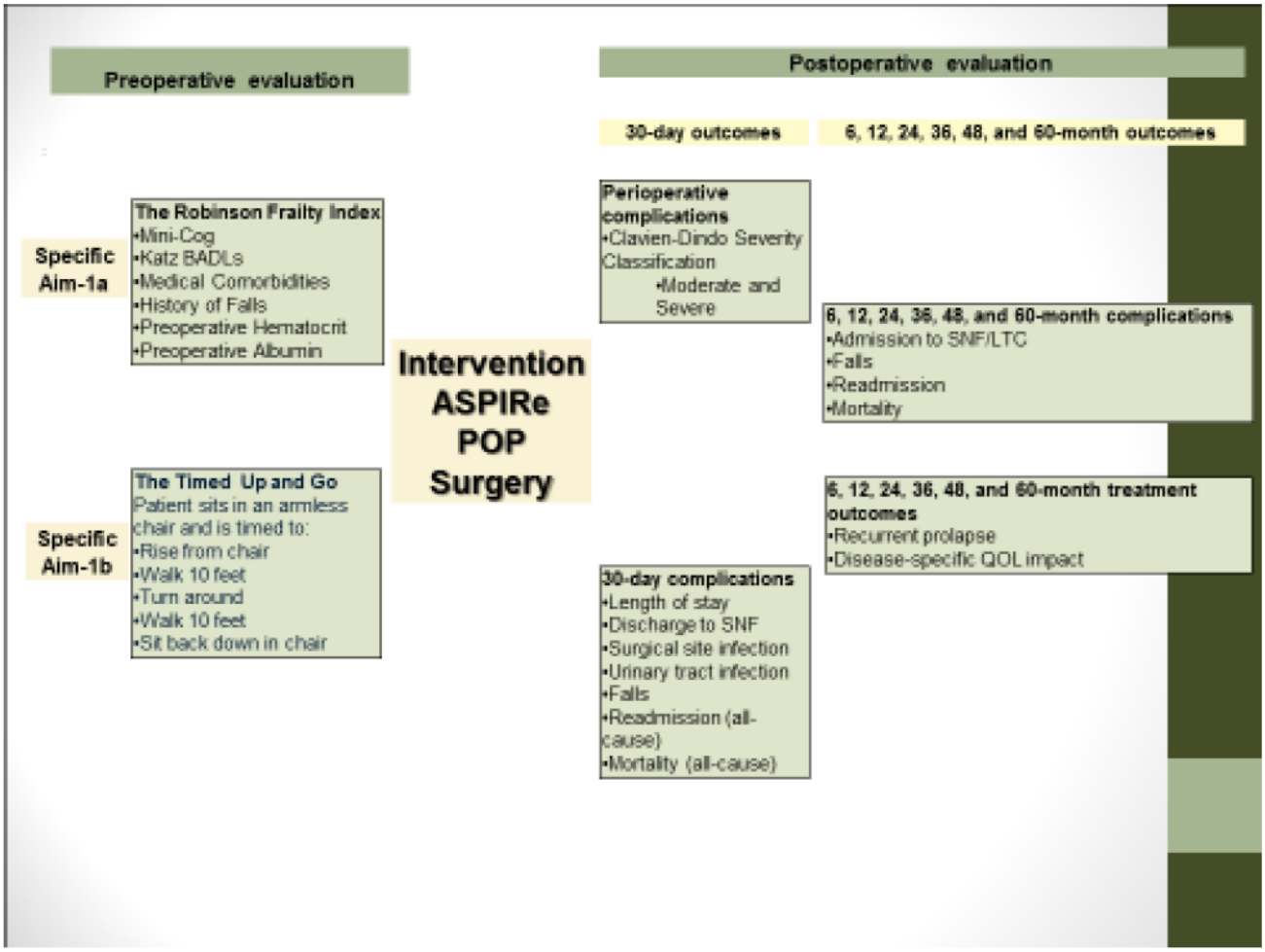
Appendix B-3: PPAR Inventory: Adverse Symptoms and Events for PPAR Capture

Adverse Symptoms	Description	PPAR Questions for Adverse Symptoms	Comments
Vaginal discharge		1. Frequency – (How often do you experience?) 2. Severity – (At its worst, how severe?) 3. Impact – (How much did it interfere with your usual activities?)	
De novo vaginal bleeding	New onset or persistent vaginal bleeding beyond 6 weeks.		
Pelvic pain	Any pain associated with worsening bother compared to preop occurring in the lower abdomen or genital area beyond 12 weeks postoperatively (excluding neuromuscular pain and dyspareunia).		
Dyspareunia	Any new onset pain associated with sexual activity that was not present during sexual activity preoperatively (AE = Anything other than Never).		
Stress urinary incontinence			
Urgency incontinence			
Fecal incontinence			
Constipation (new or worsening)	*New onset or worsening* condition in which medical treatment is required.		
Difficulty emptying bladder (new or worsening)	The new onset or worsening inability to completely empty the bladder during urination.		
Symptomatic mesh exposure (vaginal bleeding, problems with sexual relations etc.)			
Neurovascular event related to surgery	Numbness/weakness		

Adverse Events	Description	PPAR Questions for Adverse Events	Comments
Vaginal infection	Infection of the vagina determined by a physician using clinical or radiologic indicators to be uncommon to vagina and requiring treatment.	1. Severity 2. Impact	
Lower urinary tract infection (UTI)	UTI based on clinical judgment or confirmation of a culture proven by lab criteria also includes empiric antibiotic treatment for symptoms thought to be secondary to UTI.		*If UTI meets criteria for recurrent UTI, then "recurrent UTI" becomes the event.
Other infection* (specify)	Infection diagnosed using clinical or radiologic indicators not including vaginal infection, lower urinary tract infection, pelvic infection/abscess or infection/inflammation of bone.		
Laparoscopic/robotic port site hernia			
Emergency department visit for intervention related complication			
Intraoperative or perioperative event that changed management	Cautery burn, corneal abrasion, retained foreign body, ureteral or bladder injury requiring additional surgery, conversion to open surgery, ileus, bowel obstruction, need for blood transfusion.		Should capture MI, PE, CHF, as well as more minor things if they changed management.
Return to operating room for intervention related complication			
Event requiring additional treatment for intervention related complication	Trigger point, etc.		

APPENDIX C. FRAILTY SECONDARY AIM

Figure 1. Proposed Design for FASt Aim



A. STUDY OBJECTIVES AND PURPOSE

The purpose of FASt is to determine the impact of preoperative frailty and mobility on surgical treatment outcomes and postoperative complications of older women following surgical correction of apical pelvic organ prolapse (POP). Women participating in the PFDN ASPIRe trial are well-characterized prior to surgery and reliably followed for up to 5 years after their surgical procedure representing a unique and feasible opportunity to examine these predictive tools prospectively in older women undergoing elective minimally-invasive surgery. The expected outcome of the proposed work is to elucidate better tools for gynecologic surgeons to use in the preoperative evaluation of older women and improve outcomes.

We propose to measure baseline preoperative frailty and mobility, operationally using the 6 measures of the Robinson Frailty Index and the Timed Up and Go test in women ≥ 65 years old undergoing prolapse surgery in the Pelvic Floor Disorders Network (PFDN) ASPIRe trial. Women will be followed for up to 5 years postoperatively to determine both prolapse treatment failure as well as the occurrence of common postoperative complications (including 30-day surgical site-infections, all-cause readmission rates, and admissions to skilled nurse facilities, falls and mortality).

A.1 Aims

Specific Aim 1A. Frailty

To determine the impact of preoperative frailty on postoperative complications and treatment success in older women undergoing prolapse surgery.

There is a growing body of evidence demonstrating measurements of markers of frailty predict surgical outcomes in older patients undergoing surgeries better than measurements of medical comorbidities or American Society of Anesthesiologists (ASA) status alone. (1-7) The 6 measurements of the Robinson Frailty Index (Mini-Cog score, comorbidity index, functional disability, history of falls, preoperative serum albumin, and preoperative serum hematocrit) will be measured preoperatively.

Specific Aim 1B. Mobility

To determine the impact of preoperative mobility on postoperative complications and treatment success in older women undergoing prolapse surgery.

The Timed Up and Go test is a preferred measure of mobility and has been demonstrated to predict postoperative complications in general and vascular surgery patients. (8) The Timed Up and Go test will be measured preoperatively.

A.2. Hypothesis

We hypothesize that older women (≥ 65 years old) with frailty and slow baseline mobility will have equivalent treatment success following surgical correction for POP, but are at increased risk of postoperative complications.

B. BACKGROUND AND SIGNIFICANCE

Surgical procedures for female pelvic floor disorders (PFDs) are common among older women with over 150,000 procedures for PFDs performed annually on women ≥ 65 years old. PFDs are the most common indication for gynecologic surgery in older women. The age-related onset of PFDs in women suggests that many women seeking treatment for these disorders also have a high prevalence of frailty and mobility limitations which could potentially impact the risks and benefits of different treatment options. We have demonstrated that in older women (≥ 65 years) seeking treatment for PFDs, 16.7% of women meet the strict Fried/Hopkins criteria for frailty and 21.3% screen positive for dementia. (9) We have further demonstrated that similar percentages of women with and without frailty and cognitive impairment chose surgical management, over non-surgical options, for the treatment of their PFDs. (9) To date, no study has looked specifically at baseline frailty and mobility with treatment success and postoperative outcomes in older women with PFDs.

As increasing numbers of older adults in the United States undergo surgical procedures, tools to identify and counsel patients at risk for postoperative complications and improve outcomes are needed. There is a growing body of evidence demonstrating measurements of frailty and mobility predict surgical outcomes in older patients undergoing surgeries better than measurements of medical comorbidities or American Society of Anesthesiologists (ASA) status alone. (1-7) Robinson et al. developed a predictive tool using 6 measures of frailty (Mini-Cog score, validated comorbidity index, functional disability, history of falls, preoperative serum albumin, and preoperative serum hematocrit) to predict mortality after major surgery in older patients. (1) In 2013, the 6 measures of the Robinson frailty index and the Timed Up and Go test combined were demonstrated to predict postoperative complications, better than standard risk-adjustment calculators, across surgical specialties including cardiac and colorectal surgeries. (8, 10) Both of these prospective cohort studies were performed at Veteran's Administration hospitals in an almost entirely male population.

When all the 6 Robinson frailty characteristics and the Timed Up and Go test were examined to see which had the strongest associations with postoperative complications, the Timed Up and Go test [point-estimate 13.0 (95% CI 5.1, 33.0), any functional dependence (5.7 (95% CI 2.4, 13.5), Charlson index ≥ 3 (4.0 (95% CI 1.6, 9.9), and Hematocrit ≤ 35% (3.5, (95% CI 1.4, 9.0)] were found to have the strongest associations. (11) Compromised mobility, measured as slow walking speed, can be conceptualized as representing the frail older adult as slow walking speed and has been demonstrated to be related to impaired cognition, future falls, development of functional dependence, decreased survival, and frailty.(12) The Timed Up and Go test, a preferred measure of mobility endorsed by the American Geriatrics Society. (13) There is substantial evidence that mobility is the preferred measurement of frailty, if only one thing can be measured (Table 16). (12)

Elucidating how measures of preoperative frailty and mobility can predict outcomes in low-risk elective surgeries and in women is an important next step in aging research.

Table 16. Evidence that Slow Walking Speed is Representative of the Frail Older Adult

Slow Walking Speed is Related to:	Evidence
1) Impaired Cognition (14, 15)	• Poorer memory and executive function in slow walking older adults • Slow walking speed predicts future cognitive decline

Slow Walking Speed is Related to:	Evidence
2) Future Falling Episodes (16, 17)	• Slower walking speed forecasted patients who fell in the subsequent year • Walking slowly predicted older adults with recurrent falls in the next year
3) Development of Functional Dependence (16, 18)	• Slow Timed Up and Go reflected subsequent difficulties with ADLs at 6, 12, and 18 months • Slow Timed Up and Go forecasted new difficulties with ADLs in the next 12 months
4) Decreased Survival (19, 20)	• Slower walking speed in increments of 0.1 m/s is associated with decreased survival • Slower walking speed is related to decreased survival
5) The Presence of Frailty (21)	• Slow Timed Up and Go is both sensitive and specific for identifying older adults with frailty

Adapted from Townsend NT-Advances in Surgery 2014 (12)

C. STUDY DESIGN

ASPIRe Study Design

The ASPIRe study is a multi-center, randomized, surgical trial of women undergoing surgical correction of apical prolapse remote from prior hysterectomy. Women are randomized to one of three arms: sacrocolpopexy (open, robotic or laparoscopic), native tissue repair (uterosacral ligament suspension or sacrospinous ligament fixation), or apical transvaginal mesh (Uphold LITE). The primary outcome of the ASPIRe trial is measured over time up to 60 months after surgical intervention.

Frailty ASPIRe Study (FASt) Design

This supplementary study is a prospective cohort trial of women ≥ 65 years old entering into the ASPIRe trial and undergoing surgical correction of apical prolapse. Baseline preoperative measurements of frailty and mobility will be collected, and women will be followed at the ASPIRe study follow-up visits to determine postoperative complications and treatment success.

D. STUDY POPULATION

ASPIRe Study Population

The ASPIRe study population includes women ≥ 21 years old with symptomatic vaginal prolapse after hysterectomy who desire surgical correction. The anticipated sample size for the ASPIRe protocol is 363 randomized and treated women.

Frailty ASPIRe (FASt) Population

The FASt study population will include all women ≥ 65 years old participating in the ASPIRe surgical trial for apical prolapse remote from hysterectomy.

E. INCLUSION AND EXCLUSION CRITERIA

All women age ≥ 65 years old at the time of their baseline preoperative visit for the ASPIRe protocol who are deemed eligible for participation in ASPIRe will be included in this supplemental protocol.

F. BASELINE PREOPERATIVE VISIT

The 6 Robinson frailty measurements and the Timed Up and Go test will be collected at the baseline study visit. These measurements are described in Table 17. Some, but not all, Robinson frailty measurements are being collected at the time of baseline assessment as a part of the full ASPIRe protocol. This includes the collection of medical comorbidities using the Functional Comorbidity Index (heart disease, stroke, diabetes mellitus, lung disease, and arthritis).

Additional measurements required at the time of baseline visits that are unique to the FASt protocol include the Katz ADL Score, Mini-Cog exam, a single question on falls in the last 6 months, blood draw to measure serum albumin and hematocrit, and the Timed Up and Go test.

The Mini-Cog exam requires a participant to remember 3 words (e.g. Bicycle, Honesty, Yellow) and then draw a clock face at a specified time (e.g. 10 minutes to 11). The participant has 2 minutes to draw the clock face and is then asked to recall the 3 words.

The Timed Up and Go Test requires an armless chair and a place for the patient to walk 10 feet and turn around and sit down. Walking aids are allowed and no instructions are given to the patient about the use of their arms. Examiners will note if patient walks unsteadily or requires the use of a walking aid (e.g. cane or walker) to complete the task.

Table 17. Preoperative Assessments: The Robinson Frailty Index

Frailty	Scale Explanation	Score	Cut-off	Points	Harmonization
Mini-Cog	3-item recall (1 point per item) paired with clock drawing test (2 points)	Scores range from 0 (impaired cognition) to 5 (normal cognition)	< 4	1	2 questions with a time limit of 3 minutes
Katz ADL Score	1 point for each of six basic ADLs that patient is able to perform independently (bathing, dressing, toileting, transferring in/out of bed, walking, and feeding)	Scores range from 0 (totally dependent) to 6 (independent)	< 6	1	6 questions at baseline assessment
Functional Comorbidity Index	16 items medical comorbidity assessment	Scores range from 0 (no comorbid conditions) to 33 (severe co-morbidity)	≥ 3	1	Asked with main ASPIRe protocol
History of Falls	Recorded answer to the question "How many times have you fallen in the last 6 months?"		≥ 1 fall	1	Single question
Preoperative Serum Albumin	Indicative of poor nutritional status		≤ 3.3 g/dL	1	Single blood draw
Preoperative Serum Hematocrit	Indicative of anemia of chronic disease		< 35%	1	Single blood draw
Mobility	**Scale Explanation**	**Score**	**Cut-off**		**Harmonization**
Timed Up and Go*	Patient sits in an armless chair and is timed to: 1) Rise from chair 2) Walk 10 feet 3) Turn around 4) Walk 10 feet 5) Sit back down in chair	≤ 10 seconds (fast) 11-14 seconds (intermediate) ≥ 15 seconds (slow)	≥ 15 seconds	1	Single test. Examiner will record if patient walks unsteadily or requires the use of a walking aid.

*walking aids are allowed and no instructions are given to the patient about the use of their arms

G. OUTCOME VISITS

According to the ASPIRe protocol, outcome visits will occur every 6 months up to a maximum of 60 months. These visits are scheduled to assess for both the primary outcome measures of the full ASPIRe protocol (treatment failure) and secondary outcome measures (e.g. efficacy, safety and complication monitoring). In addition to the standard monitoring, the FASt protocol will specifically inquire about standard geriatric morbidity including falls, skilled nursing facility (SNF) admission.

H. TIMELINE OF VISITS AND STUDY SCHEDULE

No additional or extra visits will be required of the FASt participants beyond what is planned in the ASPIRe protocol. Three extra questions will be asked of the FASt participants at ASPIRe study visits that have already planned to assess functional status.

Table 18. Timeline of Visits and Study Schedule

	Timeline of Measures												
Measure	Base-line	Peri-Op	6 Wks	6 M	12 M	18 M	24 M	30 M	36 M	42 M	48 M	54 M	60 M
Demographics	X												
Medical History	X												
Operative and Perioperative		X											
Postoperative Review *			X										
POP-Q	X			X	X	X	X	X	X	X	X	X	X
AE Review		X	X	X	X	X	X	X	X	X	X	X	X
Mesh Exposure			X	X	X	X	X	X	X	X	X	X	X
PFDI- Q #3				X	X	X	X	X	X	X	X	X	X
PFDI-20	X			X	X	X	X		X		X		X
Katz ADL	X												
Mini-Cog	X												
Hematocrit	X												
Albumin	X												
Timed Up and Go	X												
Question about falls	X		X	X	X		X		X		X		X
Question about SNF/LTC admission			X	X	X		X		X		X		X
Question about hospital admission (all-cause)			X	X	X		X		X		X		X

*postoperative review will include dates that will allow for calculation of 30-day postoperative complications

I. OUTCOME MEASURES

I.1. PRIMARY OUTCOME MEASURES

The main outcome measure in the FASt protocol will be moderate to severe postoperative complications according to the Clavien-Dindo Severity Classification. (22) Common geriatric perioperative complications (falls and discharged to skilled nursing facility (SNF)) and 30-day postoperative outcomes (surgical site infections, urinary tract infections, all cause readmission, and mortality) will also be assessed. 30-day postoperative complications will be obtained from perioperative assessment as well as the 6-week postoperative visit. Using 30 days as a standardized time-frame for major postoperative complications, including infection, readmission, and mortality, have been widely utilized in both cardio-thoracic and general surgery literature and is currently the accepted practice for many postoperative outcome measures for surgical quality. We propose this 30-day time frame to be able to better make future comparisons of our cohort of well-selected women undergoing elective POP surgery compared with other, likely more morbid, surgical procedures and populations.

Mid and long-term follow-up will be obtained with simple questions at the 6, 12, 24, 36, 48 and 60 month visits. This will include specific questions regarding new admission to SNF/long-term care (LTC), falls, all-cause hospital admissions, and mortality will also be measured and analyzed. Data obtained from these more specific geriatric complications will be harmonized with existing ASPIRe measures.

I.2. SECONDARY OUTCOME MEASURES

Secondary outcome measures will relate to treatment success of prolapse surgery.

Treatment failure will be defined the same as the ASPIRe protocol primary outcome measure.

The participant will be considered a treatment failure if any ONE of the following criteria is met:

1) Report of bothersome vaginal bulge symptoms
2) Retreatment for prolapse (surgery or pessary)
3) Any prolapse measure (Ba, C, Bp) is beyond the hymen (i.e. > 0)

Bothersome vaginal bulge symptoms = positive response to Question 3 of the PFDI-20: Do you usually have a bulge or something falling out that you can see or feel in your vaginal area?

Participants not considered a treatment failure for the primary outcome will be considered a treatment success.

J. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

The total expected sample size for the ASPIRe protocol is 363 randomized and treated women. Prior PFDN trials have been highly successful in recruiting older women. Thirty-nine percent (n/N = 550/1407) of women were ≥ 65 years in the CARE, OPUS, OPTIMAL, and ROSETTA trials (Table 19). **Therefore, we expect approximately 142 women (39.2% x 363 women) recruited for the ASPIRe trial to be ≥ 65 years old.**

Table 19. Women ≥ 65 Years Old Participating in PFDN Trials

	Total Participants (N)	≥ 65 Years Old n (%)
CARE	321	134 (41.7)
OPUS	335	127 (37.9)
OPTIMAL	365	106 (29.0)
ROSETTA	380	182 (47.9)
Total	**1,401**	**550 (39.2)**

In a combined analysis of the CARE and SISTEr trials, the occurrence of moderate to severe postoperative complications (Clavien-Dindo Grade 2, 3 or 4) were present in 34% of women. (23) Using the strict Fried/Hopkins frailty phenotype definition, our work demonstrates that frailty is present in 17% of older women seeking treatment for PFDs. (9) The Robinson frailty score is much more liberal, considering both cognitive function as well as serum laboratory values, with 58% of patients ≥ 65 years old undergoing elective colorectal surgery and 56% of patients ≥ 65 years old undergoing elective cardiac surgery considered frail. (12)

If we estimate that 40% of women (≥ 65 years old) in the ASPIRe cohort will meet the Robinson definition of frailty and that the occurrence of postoperative complications among frail women will be 34%, we would need **134 women (54 frail and 80 non-frail women)** to detect a 20% difference in postoperative complications between frail and non-frail women (α = 0.05; power = 0.8, one-sided).

If we estimate 50% of women (≥ 65 years old) in the ASPIRe cohort will meet the Robinson definition of frailty and that the occurrence of postoperative complications among frail women will be 34%, we would need **130 women (65 frail and 65 non-frail women)** to detect a 20% difference in postoperative complications between frail and non-frail women (α = 0.05; power = 0.8, one-sided).

If we estimate that 60% of women (≥ 65 years old) in the ASPIRe cohort will meet the Robinson definition of frailty and that the occurrence of postoperative complications among frail women will be 34%, we would need **139 women (83 frail and 56 non-frail women)** to detect a 20% difference in postoperative complications between frail and non-frail women (α = 0.05; power = 0.8, one-sided).

We estimate that 142 participants recruited in the ASPIRe protocol to be ≥ 65 years old at the time of their baseline perioperative assessment.

K. ETHICAL CONCERNS AND INFORMED CONSENT

Obtainment of baseline preoperative frailty measurements present no more than a minimal increase of risk to participants participating in the ASPIRe study and these frailty measurements are very similar in risk to the other baseline measurements planned in the full ASPIRe study protocol. Therefore, we suggest that the consent for the ASPIRe trial will be adequate and an additional consent form for this supplementary study will not be necessary.

Surgeons may or may not advise and treat women differently knowing the results of their baseline preoperative frailty measurements. As frailty has not been prospectively studied in women undergoing gynecologic surgery, we do not know the impact frailty has on postoperative outcomes in older women undergoing these minimally-invasive and elective procedures. Therefore, we plan that surgeons recruiting and operating on

women in the ASPIRe study are blinded to the baseline preoperative frailty measurements.

REFERENCES

1. Robinson TN, Eiseman B, Wallace JI, Church SD, McFann KK, Pfister SM, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg. 2009 Sep;250(3):449-55.
2. Robinson TN, Wu DS, Stiegmann GV, Moss M. Frailty predicts increased hospital and six-month healthcare cost following colorectal surgery in older adults. Am J Surg. 2011 Nov;202(5):511-4.
3. Robinson TN, Wallace JI, Wu DS, Wiktor A, Pointer LF, Pfister SM, et al. Accumulated frailty characteristics predict postoperative discharge institutionalization in the geriatric patient. J Am Coll Surg. 2011 Jul;213(1):37,42; discussion 42-4.
4. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: Morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc. 2005 Mar;53(3):424-9.
5. Dasgupta M, Rolfson DB, Stolee P, Borrie MJ, Speechley M. Frailty is associated with postoperative complications in older adults with medical problems. Arch Gerontol Geriatr. 2009 Jan-Feb;48(1):78-83.
6. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010 Jun;210(6):901-8.
7. Kim SW, Han HS, Jung HW, Kim KI, Hwang DW, Kang SB, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. JAMA Surg. 2014 Jul;149(7):633-40.
8. Robinson TN, Wu DS, Sauaia A, Dunn CL, Stevens-Lapsley JE, Moss M, et al. Slower walking speed forecasts increased postoperative morbidity and 1-year mortality across surgical specialties. Ann Surg. 2013 Oct;258(4):582,8; discussion 588-90.
9. Erekson EA, Fried TR, Martin DK, Rutherford TJ, Strohbehn K, Bynum JP. Frailty, cognitive impairment, and functional disability in older women with female pelvic floor dysfunction. Int Urogynecol J. 2014 Dec 17.
10. Robinson TN, Wu DS, Pointer L, Dunn CL, Cleveland JC,Jr, Moss M. Simple frailty score predicts postoperative complications across surgical specialties. Am J Surg. 2013 Oct;206(4):544-50.
11. Robinson TN, Wallace JI, Wu DS, Wiktor A, Pointer LF, Pfister SM, et al. Accumulated frailty characteristics predict postoperative discharge institutionalization in the geriatric patient. J Am Coll Surg. 2011 Jul;213(1):37,42; discussion 42-4.
12. Fau TN, Robinson TN. Does walking speed predict postoperative morbidity? Advances in surgery JID - 0045335. 1023.
13. Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB,Jr, Walston JD, et al. Designing randomized, controlled trials aimed at preventing or delaying functional

decline and disability in frail, older persons: A consensus report. J Am Geriatr Soc. 2004 Apr;52(4):625-34.

14. Donoghue OA, Fau HN, Fau SG, Cronin HF, O'Regan CF, Kenny RA. Association between timed up-and-go and memory, executive function, and processing speed. Journal of the American Geriatrics Society JID - 7503062. 1130.
15. Katsumata YF, Todoriki HF, Yasura S Fau - Dodge, Hiroko,H., Dodge HH. Timed up and go test predicts cognitive decline in healthy adults aged 80 and older in okinawa: Keys to optimal cognitive aging (KOCOA) project. Journal of the American Geriatrics Society JID - 7503062. 0112.
16. Viccaro LJ, Perera S Fau - Studenski, Stephanie,A., Studenski SA. Is timed up and go better than gait speed in predicting health, function, and falls in older adults? Journal of the American Geriatrics Society JID - 7503062. 0726.
17. Lin MR, Fau HH, Fau HM, Fau WH, FaU WY, Huang FC. Psychometric comparisons of the timed up and go, one-leg stand, functional reach, and tinetti balance measures in community-dwelling older people. Journal of the American Geriatrics Society JID - 7503062. 0914.
18. Wennie Huang WN, Perera SF, VanSwearingen JF, Studenski S. Performance measures predict onset of activity of daily living difficulty in community-dwelling older adults. Journal of the American Geriatrics Society JID - 7503062. 0923.
19. Studenski S, Perera SF, Patel KF, Rosano CF, Faulkner KF, Inzitari MF, et al. Gait speed and survival in older adults. JAMA JID - 7501160. 0107.
20. Laukkanen P, Heikkinen EF, Kauppinen M. Muscle strength and mobility as predictors of survival in 75-84-year-old people. Age and ageing JID - 0375655. 0328.
21. Savva GM, Fau DO, Horgan FF, O'Regan CF, Cronin HF, Kenny RA, et al. Using timed up-and-go to identify frail members of the older population; association between timed up-and-go and memory, executive function, and processing speed. Journal of the American Geriatrics Society JID - 7503062. 1130(1758-535).
22. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The clavien-dindo classification of surgical complications: Five-year experience. Ann Surg. 2009 Aug;250(2):187-96.
23. Gutman RE, Nygaard IE, Ye W, Rahn DD, Barber MD, Zyczynski HM, et al. The pelvic floor complication scale: A new instrument for reconstructive pelvic surgery. Am J Obstet Gynecol. 2013 Jan;208(1):81.e1,81.e9.

ADDENDUM: EXTENSION OF THE **A**pical **S**uspension Repair for Vault **P**rolapse **I**n a Three-Arm **R**andomize**d** Trial Design (ASPIRe) STUDY FOR LONG-TERM FOLLOW-UP (E-ASPIRe)

Background

The primary purpose of ASPIRe was to determine if apical transvaginal mesh placement is non-inferior to sacral colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse and to determine if mesh reinforced repairs performed by abdominal or vaginal approach are superior to native tissue vaginal repair. Given ASPIRe was a three-arm randomized clinical trial, there were three primary aims. *Primary aim 1* was to determine if Apical Transvaginal Mesh is non-inferior to Sacral Colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years. In the case where Apical Transvaginal Mesh is shown to be statistically significantly non-inferior to Sacral Colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years, to determine if Apical Transvaginal Mesh is superior to Sacral Colpopexy for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years. *Primary aim 2* was to determine if Sacral Colpopexy is superior to Native Tissue Repair for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years. *Primary aim 3* was to determine if Apical Transvaginal Mesh is superior to Native Tissue Repair for anatomic correction of post-hysterectomy vaginal vault prolapse at time points through 3 years.

Given that in prolapse surgery there is increased awareness of adverse events and prior PFDN prolapse trials have revealed that patients may "wobble" in and out of failure both by objective and subjective criteria, we believe it is important to follow subjects that have been declared a failure during ASPIRe.

This study has thus far demonstrated excellent follow-up similar to other PFDN prolapse studies including OPTIMAL and SUPeR trials. What has become apparent with this excellent follow-up is that the ASPIRe cohort represents a unique opportunity to understand the longer-term efficacy and safety outcomes of a native tissue repair, transvaginal mesh, and abdominal sacral colpopexy for post-hysterectomy apical (vault) prolapse. There are limited studies in the literature with such outstanding long-term follow-up over an extended period. One example is the NICHD SUPeR trial performed by the PFDN. The SUPeR trial is a multicenter prospective randomized trial involving 180 subjects with symptomatic uterine prolapse who underwent either uterine conservation transvaginal mesh repair or a vaginal hysterectomy with a native tissue apical suspension. The SUPeR study was addended to follow subjects for 10 years. Given the FDA announcement in April 2020 and the increased public and media concerns with patient safety involving surgical procedures involving women's health, especially those utilizing synthetic mesh, it is essential that this trial is extended and funded to obtain additional long-term safety and efficacy data. Given the NIH proposed changes in clinical networks and the current environment and concerns with adverse events related to synthetic mesh, it is doubtful that we will ever again have the ability to obtain outcomes ranging from 7.5 to 10 years from a randomized surgical trial for women with pelvic organ prolapse. We cannot let this opportunity and all the subjects' hard work and dedication slip by and be forever lost.

Objective of Amendment/Extension

This amendment proposes to continue to follow the efficacy and safety outcomes of subjects in the original ASPIRe study for an additional 4.5 years. This will include a safety analysis performed mid-study (2.5 years).

Eligibility

Participants will be evaluated for eligibility at their last ASPIRe visit. Participants are not eligible for this study if:

- They have undergone reoperation for prolapse during ASPIRe.
- They did NOT receive one of the three treatment arms in the study.

Participants who did not complete ASPIRe and do not meet the above two exclusion criteria are eligible to participate in a limited virtual capacity described below.

Follow Up and Study Halting Rule

Follow up for each participant will last until one of the following:

- Average of 4.5 years of additional follow-up after completion of ASPIRe
- Reoperation for prolapse
- Retention rate for E-ASPIRe falls below 60% (calculation defined below)

If overall participant retention rate (in the full and virtual participants combined) ever drops below 60%, the study will be terminated so that unnecessary burden without appreciable benefits is not placed on the participants or the study investigators. This retention rate denominator will be based on the number of patients eligible for E-ASPIRe (see Eligibility section above) and excludes any deaths that occurred during the ASPIRe or E-ASPIRe study.

Visit Schedule

To decrease subject burden, the frequency of study visits will be reduced from every 6 months to annually from the date of surgery, after the last subject reaches a minimal of 3-year follow-up or the subject completes her 5-year ASPIRe last visit. A reduction of select secondary patient reported outcome measures that are unlikely to provide interesting data during this 4 to10-year time period is proposed. This will decrease study costs and subject burden, which we believe will improve follow up compliance.

The annual follow-up visits for year 6 would begin March 2022 when our first subject reaches the 6-year mark. The ASPIRe study will be in follow-up until June 2022 which would allow follow-up to continue into year 6 for patients randomized the first 15 months of the trial. If all subjects are followed for an additional 4.5-year follow-up with 6 months allowed for data analysis, the study completion date will be June 30th, 2027. The percentage of possible participants completing years 7 through 10 is outlined in table 1. The additional funding for 22 patients to perform year 6 follow-up has been reserved in budget planning for cycle 4 to include the one-year extension. In addition, the PFDN has been awarded a one-year extension extending to June 30th, 2022 by NICHD, which will allow completion of ASPIRe. The budget for E-ASPIRe will include the costs to complete follow-up for 4.5 years of the entire cohort, which

would be December 31st, 2026. Table 1 represents the abbreviated outcome measures that will be collected at each annual visit.

Table 1: Outcome measures for E-ASPIRe full participation

Measure	Year 1	Year 2	Year 3	Year 4	Year 5 (as applicable)
POPQ	X	X	X	X	X
AE review	X	X	X	X	X
Exam for mesh exposure	X	X	X	X	X
PFDI-20 (includes POPDI-6, CRADI-8, UDI-6)	X	X	X	X	X
PFIQ	X	X	X	X	X
PGI-I	X	X	X	X	X
PISQ-IR	X	X	X	X	X
SF-12	X	X	X	X	X
Patient Regret & Satisfaction (DRS-PFD/SDS-PFD)	X	X	X	X	X

Note: This represents annual follow-up visit after completion of ASPIRe (Starting between postoperative year 4 to 6.

The measures that are unlikely to add significant value to the outcome measures and have been removed from these annual assessments are:

- Functional Activity Scale
- Surgical Pain Scale
- Body Part Pain Score
- Body Image Pelvic Organ Prolapse (BIPOP)

Limited (Virtual) Participation Option

The following participants can be offered the opportunity to consent to limited E-ASPIRe participation:

- participants who discontinued from ASPIRe for the following reasons:
  - withdrew consent
  - were withdrawn by investigator
  - were lost to follow-up during the ASPIRe study
- participants who initially declined to enroll in the full, in-person E-ASPIRe.

Each of these participants will be approached so as not to introduce bias, provided that the local site IRB determines it is appropriate to approach these participants for consent to this

alternative less burdensome option. The limited study participation option excludes the in-person visit and physical exam and includes study assessments that can be completed remotely (i.e., via phone, mail, or internet.) However, subjects that present for in person routine clinical care to study sites will have objective measures performed and this information entered along with their subjective information. The objective measures obtained during routine clinical care in person visit is considered standard practice which includes physical examination (POP-Q) and assessment for mesh and suture exposure. No additional objective measures will be obtained or tracked for study purposes. Given that women with pelvic floor disorders are commonly present to pelvic floor clinics for care and these women are still enrolled in E-ASPIRe, the protocol committee believes this is appropriate to include in the limited participation cohort of subjects. Table 2 represents the outcome measures that will be collected at each annual visit under the limited participation option.

Table 2: Outcome measures for E-ASPIRe limited participation

Measure	Year 1	Year 2	Year 3	Year 4	Year 5 (as applicable)
AE review	X	X	X	X	X
PFDI-20 (includes POPDI-6, CRADI-8, UDI-6)	X	X	X	X	X
PFIQ	X	X	X	X	X
PGI-I	X	X	X	X	X
Patient Regret & Satisfaction (DRS-PFD/SDS-PFD)	X	X	X	X	X
PISQ-IR	X	X	X	X	X
POP-Q/Exam for mesh exposure	As available	As available	As available	As available	As available

Note: This represents annual follow-up visit after completion of ASPIRe (Starting between postoperative year 4 to 6. POP-Q and exam for mesh exposure will be performed when and if subject presents for clinical care during this time period.

Adverse Event Collection and Reporting

The E-ASPIRe study, the follow-up after ASPIRe last visit, is an observational extension of the original ASPIRe protocol and does not involve a treatment intervention. A primary goal of E-ASPIRe is to ascertain the long-term failure rates and safety as measured by adverse events associated with three apical suspensions using for post-hysterectomy vaginal vault prolapse. Therefore, negative outcomes that may be related to these procedures, as evidenced by treatments or re-operation for prolapse or incontinence, suture or mesh erosions, and periurethral implants for stress incontinence (such as bulking agents) will be collected by the study coordinator at the time of the annual visit and reported to the DSMB in summary format. Similarly, any additional pelvic (urologic, colorectal, and gynecological) surgery will be collected annually and reported to the DSMB in summary format.

Open-ended adverse events that are ***not*** likely related to native tissue repair or mesh-based repair either vaginal or abdominal (i.e., non-urologic/non-colorectal/non-gynecologic diagnoses, procedures and hospitalizations) will ***not*** be collected. Reportable Serious adverse events in E-ASPIRe are limited to all deaths and SAEs that are considered related to the index surgery of ASPIRe or the pelvis, and will be reported to the Medical Safety Monitor, DSMB, site IRB (per local IRB requirements), and NICHD in an expedited manner. By definition, as E-ASPIRe starts after completion of ASPIRe, a minimum of 3 years after surgery, fatalities are unlikely to be related to native tissue repair, transvaginal mesh or abdominal sacrocolpopexy in E-ASPIRe, but all fatalities regardless of relationship to the study surgeries will be collected for E-ASPIRe.

Statistical Considerations

The denominator for retention rate calculations will be based only on those eligible for E-ASPIRe who has not died (see eligibility requirements in paragraphs above). Projections based on the E-SUPeR 5-year study suggest that approximately 15% of participants eligible for the extended follow up will refuse enrollment or not be available for in-person follow up. In addition, approximately 15% of participants discontinued during SUPeR. The rate of limited participation in this combined 30% of participants is not yet available. If half are willing, then we expect 85% initial retention rate at the beginning of E-ASPIRE. Extending the study by 4.55 years with a halting rule activated at 60% retention allows for further loss to follow up of a maximum of 25% (or 5% per year of the extension). Based on the distribution of enrollment over the three-year enrollment period from ASPIRe, the median maximum follow-up at the end of E-ASPIRe will be 9 years (Table 3).

Table 3: The estimated distribution of follow up timepoints for possible participants at completion of data collection for E-ASPIRe

Years from Surgery at study completion (data collection ending 2026)	Estimated Percentage of Participants
7	11%
8	33%
9	35%
10	22%
Total	100%

There continues to be concerns with patient safety associated with the use of synthetic mesh in prolapse repairs. At this time, the results of the ASPIRe trial is unknown and E-ASPIRe will have oversight from a DSMB, but the protocol committee has elected to include a mid-study analysis for safety with assessment of adverse events. If this analysis reveals any additional important information not seen in ASPIRe, this information will be reported by the most appropriate means. The primary study outcomes will be reported after completion of E-ASPIRe.

Once the study is completed, differences between the treatment groups in long-term surgical success and other secondary safety and efficacy outcomes will be evaluated using statistical methods consistent with the analyses performed in the original ASPIRe study, as specified in protocol section M3.

Budget Considerations

The budget will be calculated on an additional 4.5 years of follow-up. Our projection models will assume 85% of the initial ASPIRe cohort will enroll in E-ASPIRe with 5% loss annually. We anticipate that 15% of participants will continue the trial in the limited participation follow up group. See attached E-ASPIRe budget.