A Randomized Trial of Vaginal Surgery for Uterovaginal Prolapse: Vaginal Hysterectomy With Native Tissue Vault Suspension vs. Mesh Hysteropexy Suspension (SUPeR)

NCT01802281

Protocol Version 5.0

October 9, 2020

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Short name: Study of Uterine Prolapse Procedures- Randomized Trial "SUPeR"

Concept approval: July 21, 2011
Mini-protocol approval: April 27, 2012

Final approval: July 20, 2012

Proposed amendment: October 9, 2020

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A. Study Aims

The primary purpose of this randomized clinical trial is to compare the effectiveness and safety of two transvaginal apical suspension strategies for uterovaginal prolapse: a mesh augmented hysteropexy vs. vaginal hysterectomy and uterosacral ligament suspension.

A.1 Primary Aim

1. To determine whether treatment success in women with symptomatic uterovaginal prolapse undergoing transvaginal mesh augmented hysteropexy differs in women undergoing vaginal hysterectomy and native tissue cuff suspension at time points through 3 years.

Hypothesis –

1. This study will test the null hypothesis that treatment success will not differ in women with symptomatic uterovaginal prolapse undergoing vaginal surgery with a synthetic mesh hysteropexy compared to women undergoing vaginal hysterectomy with native tissue vaginal suspension against the alternative hypothesis that success does differ for the treatment regimens. Operationally, the hypothesis will be tested using a two-sided log-rank test to test for a difference in the risk of failure across the two treatment arms to achieve an overall Type I error rate of 0.05 across the interim and final analyses.

A.2 Secondary Aims

1. **Secondary Efficacy Outcomes**: To compare detailed anatomic and comprehensive functional outcomes (including prolapse, urinary, sexual, bowel and health-related quality of life (HRQOL)) in both groups.

2. **Safety**: To measure and compare safety, adverse events (including mesh erosion and exposure), pain, and need for subsequent procedures in both groups.

3. **Predictors of Poor Outcomes**: To determine if advanced prolapse, age, obesity, smoking, menopausal status, estrogens, previous prolapse surgery, and physical activity levels, alone or in combination, predict higher treatment failure.

4. **Cost-Effectiveness**: To compare the cost-effectiveness of the two surgical approaches and relate the difference in cost of care between the two groups to differences in health utilities and health-related quality of life.

5. **Body Image**: To describe changes in body image as measured by a validated scale, the Body Image Scale (BIS),.in a group of women undergoing mesh augmented hysteropexy or vaginal hysterectomy and to evaluate whether or not changes in sexual function are associated with changes in body image.

B. Background and Significance

The apex of the vagina (either cervix or the vaginal cuff) is thought to be the keystone of pelvic organ support. Loss of apical support is usually present in women with prolapse that extends beyond the hymen.[1,2] At least half of the observed variation in anterior compartment support may be explained by apical support.[3] Adequate support for the vaginal apex is thought to be an essential component of a durable surgical repair for women with advanced prolapse.[4,5] Because of the significant contribution of the apex to anterior vaginal support, surgical correction of the anterior and posterior walls may fail unless the apex is adequately supported.[6] A better term for the most common prolapse conditions would be "uterovaginal" or "cuff-vaginal" prolapse. Apical suspension procedures can broadly be separated into those performed transvaginally and those performed abdominally. Abdominal procedures are performed via laparotomy or using conventional laparoscopic or robotically assisted-laparoscopic techniques. While various abdominal and vaginal approaches exist, national data suggest that 80-90% of prolapse surgery is performed vaginally.[7,8,9] Transvaginal mesh systems were introduced to improve native tissue vaginal repairs without entry into the peritoneal cavity. FDA data released July 2011 noted that in 2010 approximately 300,000 women underwent surgical procedures to repair pelvic organ prolapse (POP), one-third used mesh, and 75% of mesh procedures were done transvaginally. This study is specifically addressing transvaginal surgical repair of uterovaginal prolapse.

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

Typical vaginal treatment options for prolapse are outlined in Table 1 below.

Table 1. Vaginal Surgery Treatment Options for Uterovaginal Prolapse (non-obliterative procedures only)

	Uterovaginal Prolapse
Native tissue options	TVH-USLS (occ. TVH-SSLS) Native tissue hysteropexy
Vaginal mesh options	Hysteropexy (mesh strap technique) (e.g. Uphold®) Hysterectomy and vaginal mesh

Native Tissue Options

Uterovaginal Prolapse: Most uterovaginal prolapse is managed with a vaginal hysterectomy, +/- anterior and posterior colporrhaphy and other repairs as indicated. With minor degrees of uterine prolapse, culdeplasties (McCall, Mayo procedures) are performed to support the apex. With more advanced prolapse, a colpopexy is often performed. The most common procedure in academic centers is an intraperitoneal colpopexy (the uterosacral ligament suspension) (see Appendix A, Figure 1). The success rates for uterosacral operations were well summarized by Barber et al in ICI Chapter for POP as outlined in Table 2.

Table 2. 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[10]	50	(6-48)	Not defined	96%	Anterior 4%	None reported
1999	Comiter[11]	100	17 (6.5-35)	Grade 0-1	96%	Apex 4%	4 (4%)
2000	Barber[12]	46	15.5 (3.5-40)	Stage 0/1 or stage 2 without symptoms	90%	Apex 5% Anterior 5% Posterior 5%	3 (6.5%)
2000	Shull[13]	289	Not stated	Grade 0-1	95%	Apex 1% Anterior 3.5% Posterior 1.4%	None reported
2001	Karram[14]	168	21.6 (6 -36)	Grade 0-1	88%	Apex 1% Anterior or Posterior 11%	11 (5.5%)
2003	Amundsen[15]	33	28 (6-43)	Stage 0 or 1	82%	Apex 6% Posterior 12%	None reported
2006	Silva[16]	72	61.2 (42-90)	Symptomatic stage 2 or greater	85%	Apex 3% Anterior 7% Posterior 14%	2 (3%)
2006	Antovska[17]	32	25 (9-42)	Stage 0 or 1	NR	Apex 0% Anterior	
2007	Wheeler[18]	35	24 (0-46)	Stage 0 apical prolapse	80%	Apex 20%	0 (0%)
2009	De Boer[19]	48	12	Stage 0-1	48%	Apex 4.2% Anterior 47.9% Posterior 14.6%	None Reported
2011	Doumouchtsis[20]	42	60	Grade 0 of vaginal vault	84.6%	Apex 15.4%	5 (11.9%)

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.

Native Tissue Hysteropexy: Limited data are available on the success of native tissue vaginal uterine suspension (hysteropexy) procedures. Sacrospinous hysteropexy was first reported in 1989.[21] One randomized controlled trial (RCT) comparing sacrospinous suspension with or without vaginal hysterectomy showed higher recurrent *apical* prolapse *without* hysterectomy (21 vs. 3%, p = 0.03) with no significant difference in recurrent *anterior* prolapse *with* hysterectomy (65 vs. 50%, p = 0.2).[22] This study was limited by 7% post randomization change in surgical plan and low numbers (only 66 total participants). Cohort studies of sacrospinous hysteropexy

suggest high apical failure rates in those with advanced prolapse, but small sample size prohibited definitive conclusions. Most of these studies used suture techniques for the sacrospinous hysteropexy, which tend to be unilateral, produce deviation of the cervix and vaginal axis and this procedure has not achieved any significant popularity in the 20 years since the initial report. There is one recently published report of a retrospective single author experience with a uterosacral hysteropexy techniques, but the pelvic organ prolapse quantification (POPQ) system was not used to measure the outcomes and the outcome assessor was often the surgeon.[23] A survey of Pelvic Floor Disorders Network (PFDN) sites reveals rare performance of this procedure (approximately 25 total in last 5 years at 3 sites). In summary, although suture vaginal hysteropexy techniques have been available for more than 20 years they are uncommonly performed and there are minimal published data on these procedures.

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."[24] The report noted that in 2010 approximately 300,000 women underwent surgical procedures to repair POP, one-third used mesh, and 75% of mesh procedures were done transvaginally. Systematic reviews by the Society of Gynecologic Surgeons (SGS) found weak evidence for improved anterior anatomy when vaginal prolapse repairs were performed with synthetic mesh compared with native tissue.[25] A systematic review of vaginal mesh kits for apical repair found they appear effective in restoring apical prolapse in the short-term, but long-term outcomes are unknown.[26]

Many urogynecologists use transvaginal mesh for apical compartment prolapse, even after the July 2011 FDA notification on transvaginal mesh for prolapse. Despite widespread use of vaginal mesh for apical support in patients with and without uteri, there is a dearth of data on the results of these procedures and systematic reviews on vaginal mesh for the apical compartment are inconclusive. Well done studies are needed on vaginal mesh for the apical compartment for patient counseling and to establish retention of the uterus as a safe and effective treatment choice.

Uterovaginal Prolapse: Vaginal mesh options for uterovaginal prolapse include hysteropexy with a mesh strap technique or hysterectomy and vaginal mesh apical suspension.

*Hysteropexy (*Mesh *Strap Technique)*: In the past, justifications for removal of the uterus include concerns regarding cervical hypertrophy, future cervical or uterine pathology, or even a non-evidenced belief that the uterus organ itself is involved in the prolapse process. Uterine pathology is rare (< 1%) in women undergoing prolapse surgery.[27] Thus, the common practice of hysterectomy at the time of vaginal prolapse repair is to facilitate apical suspension. While hysterectomy is the norm, it is not clear whether removing the uterus is necessary or leads to better results. Hysterectomy can have adverse effects; it is associated with menopause 4 years earlier than in women who did not have surgery[28] and is associated with a 2-fold risk of ovarian failure.[29] When presented with a scenario in which the participant receives preoperative counseling that the success of surgery is similar with and without hysterectomy, 66% indicated

they would decline a hysterectomy (Frick AC et al, SGS 2011). A recent review on uterine-sparing apical prolapse repair concluded that vaginal hysterectomy was not necessary.[30] One purpose of this study is to compare a uterine-sparing technique (mesh hysteropexy and other native tissue vaginal prolapse repairs) with a vaginal hysterectomy utilizing native tissue/ligament suspension and other native tissue vaginal prolapse repairs.

The concept of creating a mesh suspension bridge to support the cervix and vaginal apex to bilateral sacrospinous ligaments was initially developed by Petros[31] with the infracoccygeal sacropexy; however, the trocar delivery system and multifilament mesh resulted in unacceptably high complication rates and is no longer on the market. The concept of this procedure evolved from a trocar placed device to a trocarless placement, with the most recent product developed by Boston Scientific (Uphold® and Uphold® LITE). This procedure is performed through an anterior approach using a synthetic monofilament mesh bridge which attaches the cervix to this mesh and then bilaterally to the sacrospinous ligament (see Appendix A, Figure 1). It is essentially a mesh hysteropexy technique, although the FDA predicate approval process did not allow it to be promoted and marketed as such. The most recent FDA approval was September 14, 2011 for the Uphold® LITE Vaginal Support System indicated "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, 38% reduction in weight, a 32% reduction in surface area ratio and is blue for enhanced visibility. As most literature would suggest that lighter, larger pore size mesh is preferable and may have less stress shielding (Moalli, AUGS, 2011), these changes are all considered positive, and for SUPeR we anticipate using the Uphold® LITE product. This Uphold® procedure results in a uterus in a more midline position with bilateral mesh sacral ligaments and theoretically is less likely to have suture pullout, asymmetry or extreme posterior deviation of the uterus. These mesh strap hysteropexy techniques allow the potential for decreased operative time and morbidity associated with hysterectomy. Theoretically, mesh exposure rates may be lower with these mesh strap hysteropexy techniques because of the smaller amount of mesh material used compared to other commonly performed anterior and posterior mesh kit procedures, the mesh straps are directed away from the vagina so that the mesh can be placed distant from incision lines.

In a recently published single center study of 115 participants, 53 were Uphold® hysteropexy procedures[32] at a median follow-up of 11.8 months (range 0.4-30.9 months). Using POP-Q $\geq$ -1 to define recurrence, the combined anterior apical recurrence rate was 1.89%, including no anterior (Ba $\geq$ -1) and one apical (C $\geq$ -1). Using POPQ $\geq$ 0 there were no recurrences in Ba $\geq$ 0 or C $\geq$ 0 compartment. The mesh exposure rate was 1.9%. In the overall group of 115 participants, 13.4% (13/97) reported preoperative dyspareunia and 8.3% reported postoperative dyspareunia (8/97). Dyspareunia resolved in 12/13 with preoperative dyspareunia and was de novo in 6 participants – all 6 had perineorrhaphy. As noted earlier, over 15,000 Uphold® kits have been sold in the U.S. (personal communication 5/2011) but their usage for uterine prolapse vs. vault prolapse indications is not known. However, this number would make it significantly more common than any suture/native tissue/ligament hysteropexy technique. A

recent study of 31 women randomized to hysterectomy or hysteropexy, both using polypropylene mesh, found no significant differences in outcomes.[33, 34]

A review of clinicaltrials.gov reveals that there are 2 ongoing registered trials studying the Uphold® procedure as a hysteropexy:

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 multicenter trial is sponsored by the Foundation for Female Health Awareness and coordinated at the Cleveland Clinic with anticipated enrollment that will end in summer 2012. This study is not randomized and has a one-year outcome. Both groups retain their entire uteruses and the primary outcome is a composite outcome including cervix above the mid-vagina, absence of any prolapse beyond the hymen, absence of retreatment and absence of vaginal bulge symptoms. Secondary outcome measures include anatomic, symptomatic, short-term morbidity, pain and functional activity.

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). Found in the Australian and New Zealand Clinical Trials Registry and being performed in Victoria, Australia. This study is similar to the current protocol. Major inclusion criteria are stage > 2 symptomatic uterine descent. The primary outcome is the incidence of stage > 2 apical POP (Point C below -1 cm) at 12 and 36 months after surgery. Secondary outcomes are overall POP stage > 2, PFDI-20 measures, PFIQ 7 measures, PISQ 12 measures, and PGI-I measures.

In the VAULT study, the primary outcome of anatomic and symptomatic prolapse cure is being assessed at one year. In the HUUT study, primary outcome time points are 12 and 36 months. In December of 2011, the American Urogynecologic Society (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."[35] Vaginal mesh is probably the most controversial topic in pelvic floor disorders and a strong argument can be made that the PFDN is the best group to study it. Our network can successfully perform non-biased rigorous, long-term comparative safety and efficacy studies that are needed to comprehensively assess the role of mesh in prolapse surgery. It is acknowledged that with this study design, we will not be able to separate whether it is the hysteropexy procedure itself or the mesh component of the hysteropexy that produces the results.

Other Non-Trocar Mesh Hysteropexy Techniques: Currently, there are one trocar and 2 non-trocar techniques to perform these procedures. Besides the Uphold® device, there is one other product that allows a non-trocar attachment to the sacrospinous ligament (AMS Elevate). The PFDN UCSD site has trialed both, and the disadvantage of the AMS device is that it is not as easily replaced for suboptimal anatomic applications, although this is a minor concern. The PFDN has selected the Boston Scientific Uphold® device for this study because it has been

especially designed for uterine preservation and it is the lowest mesh load to allow this technique.

Trocar Mesh Kit Techniques: Trocar-based mesh kits attempt to accomplish a similar colpopexy to the traditional suture suspension to the sacrospinous ligament (SSL). In this study we are proposing a non-trocar approach for several theoretical reasons:

1) Trocar-based methods involve the placement of a trocar through the ischiorectal fossa, and the course of the trocar places the rectum at risk for perforation.

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 trial experience). It is the opinion of many investigators that trocar-based procedures for apical suspension will decline.

5) There is some evidence from maker evolution that trocar kits are being replaced by non-trocar kits.

Hysterectomy and Vaginal Mesh Apical Suspension: This procedure is not a commonly performed operation. The uterus is typically left in place with these vaginal mesh apical techniques in an attempt to reduce the risk of mesh erosion.[36] Mesh erosion rates are fivefold higher when hysterectomy is performed.[37] Most investigators who have completed a vaginal hysterectomy and have easy access to the uterosacral native tissues do not see added benefit to adding a mesh and would rather perform a native tissue suspension.

In conclusion, the purpose of this study is to compare vaginal hysterectomy and native tissue cuff suspension with a non-trocar mesh apical repair for uterine prolapse. At this point in time, there is no strong evidence that either uterosacral or sacrospinous ligament suspension is the better vaginal native tissue repair, but uterosacral ligament suspension is the most commonly performed operation with a vaginal hysterectomy and investigators will use that procedure for cuff suspension after hysterectomy. The protocol development team will monitor OPTIMAL study results as they become available and this recommendation is subject to change if sacrospinous ligament suspension is a clear winner over uterosacral ligament suspension in that trial. For the vaginal hysterectomy, a specific non-trocar mesh procedure will be studied, namely the Uphold® LITE procedure which will be performed according to manufacturer recommendations through an anterior transverse incision. Concomitant anterior and posterior colporrhaphy procedures will be allowed, as needed, per the judgment of the surgeon in both arms.

B.2 Rationale for Primary Outcome for this Study

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" by Barber et al.[38] 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 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 POPQ stage".[39] In this study, pooled baseline data from 322 CARE patients, 380 OPUS patients and 439 ATLAS patients were used to evaluate and compare 3 continuous summary support loss (SL) variables (which contained C point measures), POPQ 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. The authors recommended "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 state "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 problems with this approach include:

1. Most importantly, for one group in this study point C is the vaginal cuff and in the other groups it is a cervix. The cervix typically resides on the anterior vaginal wall, is often 3 cm in diameter, and in normal asymptomatic parous women or in hysteropexy patients, point C could typically be near a third or a half of -TVL while in a well-supported post hysterectomy cuff, point C = -TVL. An outcome measure using this point C measure of different anatomical structures produces an inherent bias against a group that has a cervix instead of a vaginal cuff.
2. 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.[3]
3. There are no evidence-based data at which point does "point C" become symptomatic when it is above the hymen.

For all these reasons, it is important not to base the primary outcome on a C measure that will almost certainly be lower in the group that retains a cervix. Therefore, for this study, treatment success is the primary outcome and treatment success is defined as:

1. Absence of bulge symptoms
2. Absence of retreatment
3. No prolapse past the hymen

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

B.3 Study Design – Superiority Vs. Non-Inferiority

Discussions with the protocol committee on alternative study designs reached a consensus that either group could end up superior and therefore a superiority study design is most appropriate.

RCT vs. Patient Preference Trial (PPT)

A PPT trial should be considered when the study is at risk for enrolling a set of RCT participants that is not generalizable to the population at large. An example of this was the OPUS trial where there was concern that participants with some minor incontinence concerns who otherwise met OPUS inclusion criteria would be different than the randomized group. In this study, there are not any obvious patient criteria that would select out a group that would have a bias about not participating. Since we are confining our study to women with essentially an inactive uterus, strong patient concerns about uterine symptomatology that would make non-randomized participants different should be minimized. Therefore, we think a RCT is far preferable to a PPT and makes the study design cleaner. The protocol members strongly considered other designs including cohort studies, parallel patient preference trials, and patient preference trials if futility is reached in the RCT. The group considered only a RCT would provide a meaningful addition to the current literature on mesh and hysteropexy and Level A evidence to advance the science of the field. Contingency measures to improve recruiting could be considered during the trial but an alternative trial design contingency was not favored by the protocol group.

B.4 Rationale for Including a Body Image Assessment

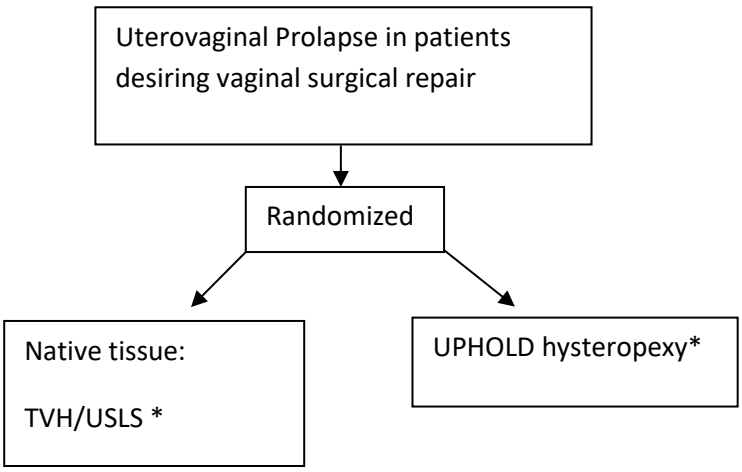
This study offers a unique opportunity to compare body image and sexual function changes in women with and without mesh, and women with and without a uterus who are treated with a prolapse procedure. While trials have been conducted randomizing women to removal or not of the cervix and have not found a difference in sexual function, there are no data regarding the sexual function of women who do and do not have their uterus removed. The physiologic role of the uterus in sexual function includes rhythmic contractions at orgasm as well as the psychological role the uterus may play in some women. In addition, body image changes have not been well-characterized in women with prolapse who then undergo treatment and body image has been shown by others to play a central role in sexual function.

C. Study Schema

The study is a multi-center, randomized, surgical trial of women with symptomatic uterovaginal prolapse desiring vaginal surgical treatment. The purpose of this study is to compare a vaginal hysterectomy with native tissue apical repairs with a non-trocar mesh hysteropexy repair. The primary outcome is measured over time (up to 60 months) using a survival analysis approach.

A figure illustrating the study design is depicted below.

C.1 Study Design Diagram



*All groups may receive concomitant anterior and/or posterior repairs as needed per the discretion of the surgeon.

D. Study Population

The study population will be adult women (≥21 years of age) with symptomatic uterovaginal prolapse at or beyond the hymen who desire vaginal surgical management. This study is intended to be done only on women who have completed childbearing and have an inactive uterus, defined as amenorrhea for 1 year. Therefore, women will be postmenopausal or will have amenorrhea from an endometrial ablation. Amenorrhea caused from exogenous steroids, or hypothalamic disorders will not allow inclusion. This protocol will adhere to the CONSORT guidelines for performing and reporting randomized controlled trials (Begg et al 1996). Women who are eligible but decline enrollment will be characterized in a manner consistent with the CONSORT requirements.

E. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were developed to be similar to the VAULT study (ClinicalTrials.gov Identifier NCT01377142) so that indirect comparisons could be made between the arms in this study and a Laparoscopic Sacral Hysteropexy group.

Inclusion Criteria

1) Women aged 21 or older who have completed childbearing
2) Prolapse beyond the hymen (defined as Ba, Bp, or C > 0 cm)
3) Uterine descent into at least the lower half of the vagina (defined as point C > -TVL/2)
4) Bothersome bulge symptoms as indicated on Question 3 of the PFDI-20 form relating to 'sensation of bulging' or 'something falling out'
5) Desires vaginal surgical treatment for uterovaginal prolapse
6) Available for up to 60 month follow-up
7) Amenorrhea for the past 12 months from either menopause or endometrial ablation
8) Not pregnant, not at risk for pregnancy or agree to contraception if at risk for pregnancy (only applicable to the rare endometrial ablation patient)
9) Eligible for no cervical cancer screening for at least 3 years[40,41]

Exclusion Criteria

1) Previous synthetic material (placed vaginally or abdominally) to augment POP repair
2) Known previous uterosacral or sacrospinous uterine suspension
3) Known adverse reaction to synthetic mesh or biological grafts; these complications include but are not limited to erosion, fistula, or abscess
4) Chronic pelvic pain
5) Pelvic radiation
6) Cervical elongation defined as an expectation that the C point would be stage 2 or greater postoperatively if a hysteropexy was performed (note: cervical shortening or trachelectomy is not an allowed intraoperative procedure within the hysteropexy treatment group)
7) Women at increased risk of cervical dysplasia requiring cervical cancer screening more often than every 3 years (e.g. HIV+ status, immunosuppression because of transplant related medications, Diethylstilbestrol (DES) exposure in utero, or previous treatment for cervical intraepithelial neoplasia (CIN2, CIN3, or cancer))

8) Uterine abnormalities (symptomatic uterine fibroids, polyps, endometrial hyperplasia, endometrial cancer, or any uterine disease that precluded prolapse repair with uterine preservation in the opinion of the surgeon

9) Indication for ovarian removal (adnexal mass, BRCA 1/2 positivity, family history of ovarian cancer)

10) Current condition of amenorrhea caused by exogenous sex steroids or hypothalamic conditions

F. Participant Screening

It is anticipated that participants will come from the practices of PFDN investigators and advertisement will not be needed. Participants with bothersome prolapse complaints and prolapse at or 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 participants desiring vaginal surgery will be offered participation in SUPeR. The pelvic organ prolapse quantitative exam and a bothersome bulge question (Question 3 of the PFDI-20) are routine clinical care and will be used to determine eligibility.

Pelvic Organ Prolapse Quantification (POP-Q)

The pelvic organ prolapse evaluation will be performed according to the guidelines established by the International Continence Society.[10] The procedure will be standardized as demonstrated in a videotape 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 POPQ examinations will be performed if maximal prolapse cannot be demonstrated in the dorsal lithotomy position.

Pelvic Floor Distress Inventory-20 (PFDI-20)

Participants will be considered as having <u>bothersome vaginal bulge symptoms</u> 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 forms.

Demographics and Medical History

- Age, race/ethnicity, marital status, education
- Obstetric history (including vaginal parity)
- Prior pelvic surgeries
- Menopause/estrogen status
- Prior treatment of pelvic organ prolapse or urinary incontinence
- Smoking
- Diabetes
- Urinary tract infection history
- Current medication use

Physical Examination

- Height and weight

Surgery should be scheduled and performed within 4 months. If more than 4 months transpires before surgery, baseline instruments will need to be re-administered.

H. Randomization

After eligibility is determined and consent is obtained from the participant, the participant will be randomized to one of the two treatment arms using a web-based randomization system. To minimize any risk of selection bias resulting from clinician knowledge of current or future treatment assignments, each participant will be randomized by the surgeon when the participant is in the operating room. The participant will be randomized to one of two apical procedures: either a vaginal hysterectomy with USLS or mesh strap vaginal hysteropexy (Uphold® procedure), with the randomized procedure provided to the surgeon for each participant individually in the operating room immediately prior to the surgery. Other native tissue vaginal wall prolapse repairs (e.g., anterior colporrhaphy, posterior colporrhaphy, perineorrhaphy) will be allowed as needed.

Randomization (1:1 to the two treatment arms) will be performed using permuted blocks, with a block size that is known only to the DCC and will be stratified by site. 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.

I. Appointment Scheduling

Routine clinical practice postoperative visits will take place during the 12 week postoperative period with the inclusion of one study visit at 6 weeks to assess for early outcomes. The 6 week in person visit and the in person visits every 6 months for the duration of the study will capture the following outcomes:

1) Urinary function including duration of post-op catheterization and de novo voiding dysfunction rates. A PVR will be assessed by catheterization or bladder scan at the 6 week visit and this is defined as an elevated postoperative post void residual > 150 ml that was not present preoperatively.

2) De novo incontinence rates and severity assessed by the UDI-6, ISI, and AE survey

3) Functional activity by administration of the Functional Activity Assessment Scale[42]

4) 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

5) Rates, location, and severity of pelvic pain using the modified Surgical Pain Scale that has demonstrated validity and responsiveness in OPTIMAL[43], pain medication use, AE survey, and Pain Mapping Instrument

6) Pelvic infection:

    a) Perioperative infections, defined as requiring antibiotics

    b) Urinary tract infections, defined as culture proven or antibiotics given

    c) Vaginal infections with flora uncommon to the vaginal canal

7) Neuromuscular problems (including groin and leg pain) with the use of the Pain Mapping Instrument

8) Vaginal scarring, vaginal shortening, de novo dyspareunia, and worsening dyspareunia with AE survey

Subsequent study visits will then occur at 6 month intervals for up to 60 months for collection of all study measures.

J. Interventions – Surgical Interventions

J.1 Surgeon Experience and Certification

Experience

To reduce bias related to surgical experience, surgeons should be experienced with all procedures being performed in this study. For the native tissue arm in this study, surgeons need to be experienced with vaginal hysterectomy and uterosacral ligament suspension and for the uterovaginal Uphold® procedures, surgeons need to be experienced with the Uphold® procedure.

In this study, all participating surgeons should be qualified to do either procedure and will require certification to be a study surgeon. Because vaginal hysterectomies and uterosacral ligament suspension procedures have been performed for decades, while Uphold® procedures are less than 4 years old, it is acknowledged that most surgeons in this study will have more experience with the TVH/USLS arm. However, the primary skills required to do the Uphold® procedure (e.g., anterior vaginal dissection to the sacrospinous ligament and the use of a Capio device) are familiar to urogynecologic surgeons and experience with these techniques is transferrable to the Uphold® 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 and signed off by the site PI and it will require the following requirements.

FOR TVH/USLS CERTIFICATION:

1. All surgeons will view a surgical videotape or DVD illustrating essential components of the uterosacral vault suspension technique.

2. All certified surgeons should have performed a minimum of 20 vaginal hysterectomies, 20 uterosacral procedures, with performance of at least 5 of these apical procedures in the 12 months prior to beginning participant enrollment.

FOR UPHOLD® CERTIFICATION

1. All surgeons will view a surgical videotape or DVD illustrating essential components of the Uphold® 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. Surgeons who meet all the criteria except the Uphold® procedure experience criteria may enroll participants in the SUPeR study; however, if the participant randomizes to the Uphold 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 uterovaginal apical suspensions that they performed outside of the SUPeR study. The surgical videotapes or DVD's illustrating essential components of the uterosacral vault suspension technique and Uphold® technique 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 videotape/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 videotape and written materials with participating surgeons at his/her site (before enrollment begins).

Certified Surgeons as Teachers

All sites in the Pelvic Floor Disorders Network are teaching institutions and have accredited fellowship programs in Female Pelvic Medicine and Reconstructive Surgery. Residents and fellows may assist at surgery for SUPeR participants. 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 uterosacral ligament suture placement, attachment of these sutures to the vagina, anterior dissection for the Uphold® procedure, Capio placement of the mesh arms, tensioning parts of either procedure, and incision closure.

J.2 Description of Surgical Procedures

Uterosacral Ligament Suspension (ULS)

The ULS procedure used in this protocol is a modification of the technique described by Shull.[13]

1. ULS 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. The type of suture material will be recorded.
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 suspension procedure will be left to surgeon preference but 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 SSLF. In the unlikely event that both ULS and SSLF cannot be performed safely or effectively, the choice of vaginal suspension procedure will be left to the surgeon's discretion and recorded.

Uphold® Procedure

The Uphold® procedure used in this protocol is a modification of the technique described by Vu and Goldberg.[32]

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 vagina wall between the bladder neck and the cervix but at least 3 cm from the cervix so that the suture line will not overlap with the mesh.
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 will be attached to the cervix with sutures.

6. Mesh modifications (e.g. cutting) are strongly discouraged; any exceptions will be documented on operative case report forms.

7. Tensioning to re-suspend the apex without tense mesh arms.

8. Vaginal closure with 2-0 polyglactin.

9. Placement of a vaginal pack and Foley catheter removed on POD1.

For all procedures:

1. The study surgeon is responsible for meeting the experience requirements, is the surgeon of record, and will be present and scrubbed in for key portions of the procedure. Residents or fellows may participate in procedures as is standard for each Clinical Site.

2. Cystoscopy with intravenous indigo carmine dye (or an appropriate substitute) performed at the end of the procedure after all vault suspension sutures are tied or after the Uphold® straps are adjusted and is required as a standard part of the surgical procedure.

3. Prophylaxis against deep vein thrombosis is required for all participants. The method may be chosen by each surgeon.

4. 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.

5. All concomitant native tissue procedures must be declared and recorded prior to randomization. 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.

6. 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. A non-straining POPQ examination will be performed and recorded at the end of the operative procedure and prior to cessation of anesthesia.

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 midurethral slings in the setting of vaginal operations for prolapse. Therefore, concomitant full length transobturator or retropubic midurethral slings will be allowed per the discretion of the surgeon. The placement of a midurethral 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.[44,45]

J.3 Masking of Randomized Intervention

Although the primary outcome does not depend on masked patients and blinded evaluators, several important patient-reported secondary aims are subject to patient reporting bias if the participant is aware of her group assignment. For example, in this current era of television advertisements recruiting patients for class action law suits against mesh manufacturers, many urinary, bowel, and sexual complaints are being attributed to transvaginal mesh and it is quite possible that if the participant knows that she has mesh she might be more likely to over-report these conditions. There are also significant internet testimonials that hysterectomy worsens sexual function and a patient's knowledge of having or not having a uterus could bias her reports on sexual function. For all these reasons, the ideal study design encourages masking and blinding to treatment assignment. There is precedent for achievable patient and evaluator blinding in RCT's of supracervical and total hysterectomies[46] and in this study, where the uterus is inactive, we think those successful blinding examples are relevant to this study design.

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. The study surgeon will not be performing the anatomic outcome assessments. It is our intent that when feasible and ethical, all outcomes assessors and the participant will be masked to the treatment allocation. All participants will be asked to remain masked to their treatment group for the duration of the study, although we recognize that unintentional unmasking by the participant may occur. Current ACOG recommendations allow women age 30 years or older with known recent negative cervical cytology and negative HPV testing to be screened no sooner than 3 years.[40] Current US Preventative Services Task Force, American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology recommendations allow no screening for age <21, every 3 year screening for ages 21-29, every 5 year screening ages 30-65, and no screening for women older than 65.[41] Therefore all participants in this study should be able to go 3 years without screening and the overwhelming majority of participants in this study will be >30 and are allowed to have every 5 year screening. Unmasking is permitted for the rare amenorrhoeic woman with a uterus aged 18-30 eligible for this study who in the opinion of the study surgeon needs screening during the study. We recognize that this masking is for cervical cancer screening and women may still have regular exams. In the event the patient is about to have a pelvic exam or imaging study of her pelvis we will request the patient to remind her provider to not tell her about the status of the absence or presence of her uterus. Participants will be encouraged to see the study team for any gynecologic problems or evaluations during the course of the study. At every 6 month visit, the participants will be queried if they are still blinded, and if not, what caused the unblinding and what group they think they are in? This will be done in a manner that reaffirms that blinding is preferred for the duration of the study. After the study is completed (maximum 60 months) participants will be queried as to what randomization arm they think they received and will then be notified of their uterine and mesh status. To minimize biases, subjective and most objective outcomes will be

obtained by study nurses or coordinators masked to the procedure. POPQ measures will be obtained by co-investigators or different study nurses who will not be blinded to the surgical procedure because they will either see or not see a cervix but would be less biased than the operating surgeon towards over-reporting the anatomic surgical outcome.

Table 3. Masking Summary

Masking	Uterovaginal Prolapse Intervention
Participant	Yes
Study coordinator or study nurse	Yes
Telephone interviewer (if applicable)	Yes
Study surgeon	No
Anatomic evaluator[#]	No[#]

[#] to maximize masking, it is proposed that the anatomic evaluator not be the study coordinator or study nurse who should remain masked. The anatomic evaluator should be a Co-investigator, fellow, or other qualified nurse who did not perform the surgery.

It is preferable to maintain masking of group assignment for participants until the study completion. There are two issues to consider: (1) masking the participant to the surgical intervention throughout study follow-up unless there are medical reasons or participant insistence to reveal assignment; and (2) masking the research staff (evaluators) who will be performing data collection for outcome measures. In addition to those described above, the following steps will be taken to maintain masking while maintaining participant safety:

- For the dictated operative note, the procedure listed under the “Procedure” heading will be indicated as “vaginal apical suspension as per SUPeR protocol.” The specific type of vault suspension will not be listed under the “Procedure” heading; however, details of the vaginal hysterectomy / vault suspension or hysteropexy will be described in the text of the detailed operative description.

- For sites with electronic medical records, all references to the vaginal apical suspension procedure will be indicated as “vaginal apical suspension as per SUPeR protocol” with the exception of the detailed operative description in the text of the dictated operative note described above.

- For the handwritten operative note in the participant’s hospital chart (if applicable), the procedure will be indicated as “vaginal apical suspension as per SUPeR protocol (see dictated operative note)”.

- The procedure on the surgical consent form (not the research consent form) will be listed as “vaginal apical suspension per SUPeR protocol.”

- The study surgeon (not the study coordinator or other research staff that will be completing postoperative data collection) will complete the intra-operative portion of the

Hospitalization Form which will be transmitted electronically to the Data Coordinating Center.

- A sticker will be placed on the participant's hospital chart, indicating that she is enrolled in the SUPeR study and that the exact type of procedures performed should not be revealed to her.
- In the case the care team needs to know the exact surgical procedure, details of the surgery can be found in the procedure details of the operative note.
- Key clinical and laboratory costs that have the potential to unmask the participant through the billing process will be covered by the research study.

If unmasking does occur, the study coordinator will complete a protocol deviation form. Deviations will be tracked and reported to the DSMB to determine if unmasking is occurring at high frequency and to determine if a pattern of unmasking can be found and addressed by protocol or policy revisions.

K. Outcome Visits

Outcome visits will occur every 6 months up to a maximum of 60 months. All women will continue to be followed through the end of the study, including those who seek alternative treatment or re-treatment to ensure that all safety events are captured. At each of these visits, a physical exam will be performed to assess anatomic (POP-Q) results and also to evaluate for mesh exposures and erosions and to ask about bulge symptoms (PFDI-Q3) and retreatment so that the primary outcome and safety outcomes will be assessed. The PFDI-Q3 has been demonstrated to function well as a standalone question and does not require the entire PFDI-20 to be administered with it.[47] Additionally at 6, 12, 24, 36, 48, and 60 months secondary outcome measures will be administered.

L. Timeline of Visits/Calls and Study Schedule

In-person visits every 6 months up to 60 months. It is not anticipated that with this frequency of in person visits there will be a need for telephone calls. Total study enrollment time is estimated to be 24 months. Based on these assumptions, an expected study schedule is included in Appendix B.

Table 4. Timeline of Measures

Measure	Base-line	Peri-op	6 wks	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo	60 mo
Demographic info	X												
Medical history	X												
Operative and perioperative review *		X											
Postoperative recovery#			X										
POPQ	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
Exam for mesh exposure			X	X	X	X	X	X	X	X	X	X	X
PFDI – Question 3	X		X	X	X	X	X	X	X	X	X	X	X
Functional Activity Scale	X		X	X	X	X	X		X		X		X
Surgical Pain Scale	X		X	X	X	X	X		X		X		X
PFDI-20 (includes POPDI-6, CRADI-8, UDI-6)	X		X	X	X	X	X		X		X		X
PFIQ	X			X	X	X	X		X		X		X
PGI-I				X	X	X	X		X		X		X
ISI	X		X	X	X	X	X		X		X		X
PISQ-IR	X			X	X	X	X		X		X		X
BIS	X		X	X	X	X	X		X		X		X
SF-12	X			X	X	X	X		X		X		X

* Includes OR complications with Dindo score, EBL, Transfusion, HGB change from pre-op to POD1, length of hospital stay.
# Assess duration of postoperative catheterization, PVR, de novo incontinence, pelvic pain scale and pain mapping review for vagina, groin, and leg pain.

M. 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.

M.1 Primary Outcome Measure

A 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) Re-treatment 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. This single question has been identified to most accurately and reliably identify those women with POP. An affirmative answer to this question was 96% sensitive (95%CI 92-100) and 79% specific (95%CI 77-92) for prolapse beyond the hymen. The 1-week test-retest reliability was good (kappa .84).[47]

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

M.2 Comparative 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: POPQ point (Ba, Bp, C), mean or median (but should be normally distributed) measures postop in each group. Proportion of participants in each group with C > -1/2 TVL.

2) Functional:

    a) Prolapse – mean Patients Global Impression of Improvement (PGI-I)[48], mean overall prolapse symptoms using POPDI-6[49] scores

    b) Urinary – urinary function including duration of post-op catheterization, mean UDI-6 scores[49], Hunskaar Incontinence Severity Index, de novo voiding dysfunction rates, de novo incontinence rates

        (i) Sexual – mean PISQ-IR[50] and specific rates of de novo dyspareunia

        (ii) Bowel – bowel function using CRADI-8 scores[49]

        (iii) QOL – general SF-12 scores and sub-scales[51], and Pelvic QOL mean PFIQ score[49]; Functional Activity Assessment Scale[42]

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 post-operative complications categorized using a modification of the Dindo Classification.[52]

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

Other complications possible in both arms:

1) Rates of pain captured from the modified Surgical Pain Scale[43], pain medication use, and location of pain with Pain Mapping Instrument

2) Pelvic infection:

   a) perioperative infections

   b) urinary tract infections

   c) vaginal infections with flora uncommon to the vaginal canal

3) Vaginal shortening, de novo vaginal bleeding, atypical vaginal discharge, fistula formation, neuromuscular problems (including groin and leg pain)

4) Need for subsequent procedures – any surgical or non-surgical treatment for pelvic floor disorders (including urinary incontinence, voiding dysfunction, defecatory dysfunction or fecal incontinence, recurrent prolapse, and dyspareunia/pelvic pain). Any subsequent uterine or cervical office or Operating Room procedure in hysteropexy group (e.g., cervical biopsy, LEEP, hysteroscopy, D and C, hysterectomy).

5) Subsequent uterine or cervical pathology

6) Rates of vaginal scarring defined as de novo vaginal scar requiring medical or surgical intervention or adversely affecting quality of life

7) Rates of vaginal shortening, de novo dyspareunia, and worsening dyspareunia with AE survey instrument

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, revision of vaginal stricture, operative hysteroscopy, or hysterectomy.
- New onset (de novo) 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 two surgical procedures to represent an important difference between groups. Stopping the study will be considered by the DSMB during their 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 two 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.

Secondary Aim 3 – Predictors of Poor Outcomes: The co-variates of advanced prolapse, age, obesity, smoking, menopausal status, estrogens, primary vs. recurrent prolapse, and physical and functional activity as measured by the Functional Activity Scale will be evaluated to determine if they predict higher treatment failure.

Secondary Aim 4 – 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 pelvic organ prolapse with native tissue surgical repair or transvaginal mesh repair and women's preference for health states for improvement in pelvic organ prolapse 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 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 case report forms 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 5. 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[53] 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.[54] 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 two 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 traditional vaginal hysterectomy with native tissue vault suspension and mesh hysteropexy suspension groups. When estimating QALYs, we will also adjust for participants' baseline utility scores to account for potential imbalance in baseline utility between the two treatment groups.[55]

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. 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.[56, 57] 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.

Secondary Aim 5 – Body Image: We will compare BIS scores between women who undergo uterovaginal prolapse repair with a mesh hysteropexy and with hysterectomy and native tissue repair.

Hypothesis: Women with uterovaginal prolapse will demonstrate improvement in body image as measured by a body image scale following surgery for uterovaginal prolapse, and will parallel changes in sexual function; both measures will improve with improvements in prolapse, as measured by the leading edge of prolapse and the POPDI.

Hypothesis: BIS scores will demonstrate greater improvement in the cohort of SUPeR women who undergo hysteropexy with mesh.

Background: Body Image is how a woman feels—her perceptions and attitudes—about her body.[58] Body image likely plays an important role in demand for treatment for pelvic organ prolapse and a woman'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.[59] Jelovsek et al modified the BIS and compared women with advanced prolapse (stages 3 and 4) to a cohort of women with normal support (stages 0 and 1). In that cross sectional cohort study, women with prolapse were more likely to be self-conscious about their body, less likely to feel physically attractive, less likely to feel feminine, and less likely to feel sexually attractive.[60] In addition, women with decreased body image also scored more poorly on the physical scale of the SF-12, a general measure of overall quality of life.[61] Further investigations have explored the interplay between body image, sexual function and prolapse in a large multi-center cohort study of 384 women undergoing surgical and non-surgical treatment for prolapse.[60, 62] At baseline, women with poorer body image reported poorer sexual function. Of the 235 women who gave data at 6 months follow-up, sexual function improved (PISQ 12 pre 33 +/- 0.6 vs. post 43 +/- 0.8, $p < .0001$) as well as changes in body image (pre 23.2 +/ 6 vs. post 12.8 +/- 3, $p < .001$) and bother from prolapse (POPDI-6 40.6 +/- 1.7 versus 14 +/- 1, $p < .01$). In a multivariate linear regression analysis, only changes in body image and body mass index remained associated with changes in sexual function.[60]

Using the *Body Exposure During Sexual Activity Questionnaire* (BESAQ) and the *Body Image Quality of Life Inventory* (BIQLI), Lowder et al compared cohort of 76 women planning surgery

for prolapse to 67 women controls with normal vaginal support.[63] BESAQ scores improved after surgery, as did measures of prolapse and sexual function on the PISQ 12; in a regression analysis, postoperative changes in POPDI scores were predictive of 6 month BESAQ scores, further demonstrating the association between prolapse and body image changes. In a follow-up qualitative study of 25 women who participated in focus groups and 27 women who participated in one-on-one interviews, women with prolapse reported they felt self-conscious, less feminine and less attractive. In addition, women reported that they often changed sexual intimacy practices because of their prolapse, or avoided intimacy altogether.[64]

While the PFDN has described changes in sexual function in women undergoing treatment for prolapse and following childbirth, these evaluations of sexual health has focused on changes in validated sexual function measures (either the PISQ 12 or the Personal Experiences Questionnaire) and change in sexual activity status and did not include measures of body image changes. SUPeR will randomize women to either a vaginal apical repair with mesh or a vaginal native tissue repair to answer the question of whether mesh augmented repair without hysterectomy leads to better prolapse outcomes than native tissue repair with hysterectomy for treatment of uterovaginal prolapse. This trial offers a unique opportunity to explore the body image changes of women following vaginal surgery for uterovaginal prolapse with and without a graft-augmented repair and to evaluate whether body image changes play a role in reports of sexual function following repair. Additionally, we will be able to add to the literature regarding the possible impact of hysterectomy on body image.

Methods: The original BIS was developed in 276 patients diagnosed with cancer and then was revised and further validated in a cohort of 682 women with breast cancer. Factor analysis of this measure revealed a scale that was resolved with a single factor that accounted for > 50% of variance in responses. The scale showed high reliability (total Cronbach's alpha 0.93), criterion and discriminant validity.[58] The original BIS included two questions which were eliminated by Jelovsek ("Have you been feeling the treatment has left your body less whole?" and "Have you been dissatisfied with the appearance of your scar?") and was reworded to be specific to prolapse (Table 6); this modified version was used in both the papers by Lowenstein. Others have used the BIS scale in a cohort of women undergoing treatment for prolapse with a pessary, and included one of the previously eliminated questions, "Have you been feeling the treatment has left your body less whole?"[65] but eliminated the item regarding the appearance of a scar. We propose to use the original BIS scale of 10 items, with the change in wording to make the scale specific to prolapse proposed by Jelovsek. The BIS scale will be administered at baseline, 6 months, 12 months, and then every 6 months until the study is concluded.

Total BIS scores will be calculated as described by Hopwood et al, and changes in BIS scores will be correlated with changes in PISQ R scores, the leading edge of prolapse, and POPDI scores using Pearson's and Spearman correlation coefficients. If measures are correlated, we will further describe changes in individual items of the BIS scale before and after treatment for prolapse, to determine which portions of the BIS scale explain the overall change in BIS scores, and evaluate the associations between BIS item scores and PISQ-IR item scores. General linear model analyses will be used to evaluate how well the combination of BIS scores, demographic and experimental variables explain changes in PISQ-IR scores.

Between randomization group comparisons will also be made using linear models for total and item scores controlling for randomization strata. We will also utilize extensions of this model to evaluate if any differences in BIS scores are either modified by or confounded with differences in either efficacy or side effects.

SUPeR will recruit 180 women. Body image will be measured in all women enrolled even though not all women will be sexually active. For the analyses described above, we anticipate that approximately 75% (135 women) will report sexual activity, and approximately half of the cohort will be randomized to the group undergoing mesh strap/uterine preservation or native tissue repair with hysterectomy. Lowenstein et al demonstrated a change in BIS scores before and after treatment for prolapse in sexually active women from 23.2 +/- 1.6 to 12.8 +/- 1.3 in a cohort of 239 women undergoing both surgical and non-surgical treatment for prolapse. Because all women in this study will undergo surgical procedures, we anticipate that differences in this study will be at least this large; consequently, assuming that approximately 130 women are sexually active, the study will have at least 90% power to detect those changes.

Table 6. Body Image Scales

#	Original Body Image Scale (BIS)	Modified Body Image Scale (MBIS)
1	Have you been feeling self-conscious about your appearance?	Same
2	Have you felt <u>less</u> physically attractive as a result of your disease or treatment?	Have you felt less physically attractive as a result of ***your vaginal prolapse***?
3	Have you been <u>dissatisfied</u> with your appearance when dressed?	Same
4	Have you been feeling <u>less</u> feminine as a result of your disease or treatment?	Have you been feeling less feminine as a result of ***your vaginal prolapse***?
5	Did you find it difficult to look at yourself naked?	Same
6	Have you been feeling less sexually attractive as a result of your disease or treatment?	Have you been feeling less sexually attractive as a result of ***your vaginal prolapse***?
7	Did you avoid people because of the way you felt about your appearance?	Same
8	Have you been feeling the treatment has left your body less whole?	Deleted
9	Have you felt <u>dissatisfied</u> with your body?	Same
10	Have you been <u>dissatisfied</u> with the appearance of your scar?	Deleted

N. Sample Size/Power Calculations

This study is designed to compare the relative effectiveness of two transvaginal apical suspension strategies for uterovaginal prolapse: a mesh augmented hysteropexy vs. vaginal hysterectomy and uterosacral ligament suspension. Power and sample size calculations were generated to determine the sample size needed to test for treatment difference favoring the mesh augmented strategy (i.e., a superiority trial) across the study arms for a variety of assumptions about effect size and study follow-up time. For all power analyses, we assumed that failure in both arms follows an exponential survival model and that the native tissue repair has a success rate of 80% at 24 months. This 80% calculation is based on an assumed 85% anatomic success rate for uterosacral ligament suspension (Table 2) and an additional 5% failure rate based on symptom failure. In the only published Uphold® series there is a 98% 12 month anatomic success rate.[32] Although no 2-year outcome data are available for the Uphold® procedure, under an assumption of a constant hazard, the 1-year success rate of 98% yields an estimated 2-year anatomic success rate of 96%; combining this estimate with a similar 5% rate for symptom failure yields a 91% composite (anatomic and symptom) success rate. All analyses also assumed that statistical tests would be conducted with a Type I error rate of 0.05 with adjustment for multiple comparisons based on a single interim analysis. Sample size estimates assumed that the 2-year success rate in the mesh-augmented arm is in the range of 90% to 93% at 24 months (note that this represents a hazard ratio in the range of 0.33 to 0.47 under the assumed exponential survival model), that the enrollment time for the study is 2 years, the loss-to-follow-up on both arms is no more than 5% per year, and the total study duration from last participant enrolled to primary outcome analysis is 36 months with one interim analyses for efficacy when the last participant reaches the 24-month follow-up. Table 7 provides estimates of the power for the different assumptions for total sample sizes in the range of 160 to 300 participants under the assumption that a single interim analysis will be conducted using O'Brien-Fleming stopping rules.

Table 7. Sample Size Calculations

Total Sample Size	**Power as a Function of 2-Year Effect Size—with Base 2-Year Success of 80% and 36-Month Follow-Up After Last Enrollment and a 2-Year Enrollment Period**			
	Δ=0.10 HR=0.472	**Δ=0.11 HR=0.423**	**Δ=0.12 HR=0.374**	**Δ=0.13 HR=0.325**
160	0.87	0.93	0.96	0.99
180	0.89	0.95	0.98	0.99
200	0.92	0.96	0.99	>0.99
220	0.94	0.98	0.99	>0.99
240	0.96	0.98	0.99	>0.99
260	0.95	0.99	0.99	>0.99
280	0.98	0.99	>0.99	>0.99
300	0.98	0.99	>0.99	>0.99

Based on these calculations, a total of 180 participants will be randomized at a 1:1 ratio to the two treatment arms. This sample size will provide a power of 0.89 to detect an additive difference of 10% in the 2-year success rate (i.e. a hazard ration 0f 0.472) and a power of 0.95

to detect additive differences of 11% or greater in the 2-year success rate (hazard ratios of 0.423 or less).

One of the advantages of the survival analysis approach is that the study continues to accumulate information on individuals enrolled early in the study as they have events beyond a fixed two-year or three-year time frame, particularly for a study like this one in which successes are more likely to occur than are failures over the first three years. As such, the survival approach with multiple looks will allow the analysis of the primary outcome of overall risk of treatment failure for the study to be completed and results published, while still collecting information on longer-term outcomes.

O. Statistical Design

Data analysis: Surgical failure rates will be compared using survival analysis approaches appropriate for interval censored data (classic log-rank tests and survival models using a generalized linear model approach with a complementary log-log link) 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. For the primary analysis we first generate a standard log-rank test to provide an overall test of difference of the two treatment regimens. We will then conduct model-based analyses using a generalized linear model with a complementary log-log link that examines failure risk as a function of treatment controlling for appropriate design variables site and age cohort). The model-based analyses will be used to generate an overall test of treatment difference using a two-sided hypothesis test with an overall Type I error rate of 0.05, and point and interval estimates of 12-, 24- and 36-month surgical success rates on each treatment arm as well as well as differences in these rates on the two arms. The study has been designed for a single interim analysis when the last participant enrolled reaches the 24-month follow-up time using a Lan-DeMets alpha spending function with O'Brien-Fleming type boundaries. This approach will result in spending approximately 0.001 alpha at the interim analysis and 0.049 at the final analysis.

Although the primary analysis will include all follow-up data from participants with follow-up time beyond 36 months when the study performs the primary analyses, 48- and 60-month data will still be limited at that time. Once all study participants have completed the 60-month follow-up period, a generalized linear model with a complementary log-log link that examines failure risk as a function of treatment controlling for appropriate design variables site and age cohort) will be used to conduct a secondary efficacy analysis to evaluate differences in long-term success between the two treatment arms. These analyses will provide an overall test of treatment difference using a two-sided hypothesis test with an overall Type I error rate of 0.05, and point and interval estimates of 48- and 30-month surgical success rates on each treatment arm as well as well as differences in these rates on the two arms.

A number of secondary outcome measures that include both continuous and binary measures will be collected periodically across the study. To account for the correlation among the multiple measures on each study and 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.

P. Ethical Concerns, Limitations, and Informed Consent

P.1 Ethical Concerns

Physician bias against uterine preservation or mesh: Physicians may be reluctant to perform a uterine sparing, mesh supporting procedure instead of the traditional vaginal hysterectomy and apical suspension. Some physicians (and patients) have strong beliefs against the use of mesh, especially in light of the July 2011 FDA warning. We note that survey results still demonstrate that many AUGS members are still doing these procedures implying that this is still a relevant surgical problem. The mesh use in this study with the Uphold® device minimizes mesh load. All other repairs will be native tissue further minimizing possible mesh-related complications. The mesh exposure rates and complications related to mesh should be low as the mesh load is small, the newer Uphold® mesh is even lighter, and it is not placed adjacent to the incision. Furthermore, mesh erosion rates requiring OR removal would likely produce a significant difference in "important complications" and could lead to early study termination. This should be acceptable to surgeon and patient. We believe that this study has equipoise given the expected similar recovery and morbidity for both procedures. If mesh apical procedures are comparable to mesh anterior compartment procedures then evidence for equipoise comes from systematic reviews[66] and an RCT[67] which already support improved anatomic outcomes with mesh in the anterior compartment. The study also has relevance given the growing trend of uterine sparing surgery and the widespread use of transvaginal mesh kit procedures.

Participant bias: Women may have preferences regarding removing or conserving their uterus. We think evidence-based counseling on the pros and cons of both these options with emphasis on the importance of studying the issue will resolve this. We note that a problem somewhat similar to this was encountered and easily overcome in the successful randomized trials of supracervical vs. total hysterectomy.[46, 68] Similarly, a successful RCT examined hysterectomy compared with endometrial ablation of dysfunctional uterine bleeding (ClinicalTrials.gov Identifier NCT00114088). At one site (UCSD), we have been presenting these 2 options to patients and have not typically encountered strong patient preferences in either direction. There is some concern that verbal reports from the Australia study have implied that patients equally choose between hysterectomy and hysteropexy, but prefer to choose rather than be randomized. We have heard of other countries and groups saying randomization in surgical trials is not possible for more than 12 years in both networks and every time this has not been our experience in our networks. We think that we will have fewer problems in this country and in this network because of our track record of effective randomization.

Masking: All efforts will be made to mask participants and outcome evaluators, but the study has inherent limitations in this regard. Participants may find details of their operation on their surgical bill, but to minimize unmasking from a bill review we will be requesting donated Uphold® kits from the manufacturer. Participants may examine themselves and feel a cervix, or

they may be told they have a cervix by another examiner. There may be health situations where it is necessary for them to know if they have a cervix and if so, they will be readily told by their study surgeon. We think it will be relatively easy to keep the study coordinator masked for ascertaining all outcomes other than the anatomic one. The anatomic outcome evaluator will need to know if the participant has a cervix or not to properly record POPQ values, but the study is designed so that this evaluator is a third person and has no bias towards the results.

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; 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. For this reason, we favor a hysteropexy kit that lends itself to standardization. It is likely that industry funding will be available for this study, but industry will not participate in data collection, data analysis, or manuscript preparation.

P.2 Informed Consent

Patients who are candidates for study participation will be approached for enrollment. Written informed consent will be obtained in accordance with Institutional Review Board guidelines.

A common template for informed consent will be used by all centers, with modifications allowed to meet the necessary requirements of their respective institutional human subjects committees.

Uterovaginal Prolapse: Eligible women will be informed that traditional treatment for uterine prolapse includes hysterectomy with native tissue suture support; but more recently an option is uterine sparing with a mesh graft suspension and we do not know which procedure is more successful or more durable. Advantages of hysterectomy include eliminating the possibility of future uterine or cervical pathology while the disadvantages are the removal of a normal organ, possible earlier menopause, and the risks of intra-peritoneal injury, intra-abdominal bleeding and vaginal shortening. The advantage of the hysteropexy procedure includes preservation of a normal organ, normal timing of menopause, and decreased risk of intra-peritoneal complications. The disadvantages include possible future uterine or cervical pathology requiring additional surgery. 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.

P.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 of the DSMB that occurs after initiation of enrollment in the trial, the DSMB will review study enrollment and participant safety information and will have 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 will be considered by the DSMB in their deliberations about study safety and futility, final stopping criteria will be established by the DSMB.

The DSMB will also review efficacy data to evaluate whether to stop the study for efficacy at the planned formal interim analysis described in Section O.

P.4 Reporting of Serious Adverse Events

Each clinical investigator is responsible for reporting serious or unexpected adverse events to the IRB at their institution and to the Data Coordinating Center, who will transmit the information to the Safety Monitor. The DCC and the Safety Monitor summarize the case and reports it to the NIH Program Director and to the DSMB Chair in an expedited manner. The Safety Monitor and Chair of the DSMB will determine whether the case should be reported to the IRBs at all the institutions participating in the trial. The Chair of the DSMB has the discretion to convene an emergency meeting of the DSMB.

Q. Protocol Costs

See separate spreadsheet.

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S. Appendices

Appendix A. Figures

Figures demonstrating the 2 operations proposed in the SUPeR protocol (illustrations by Jasmine Tan-Kim, MD).

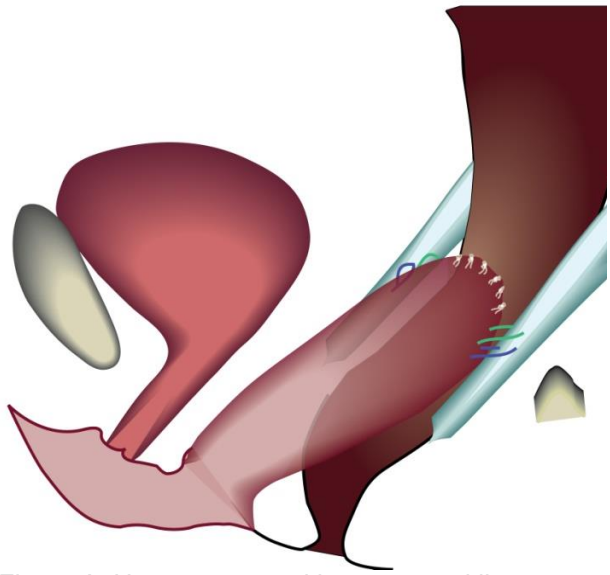

Figure A. Hysterectomy with uterosacral ligament suspension

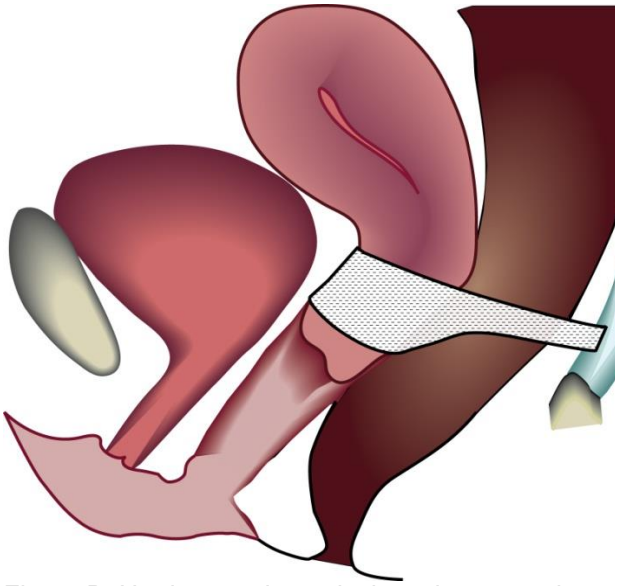

Figure B. Uterine sparing apical mesh suspension (hysteropexy)

Appendix B. Planned Study Timeline

Milestone Date	Description of Milestone
December 2012	Final Protocol Version 1.0 available for submission to FDA and site IRBs
March 2013	Randomize first participant
March 2015	Enrollment Complete
March 2017	Conduct Interim Analysis when last participant reaches 2-year follow-up
March 2018	Last participant reaches 3-year follow-up
August 2018	Final study report submitted to BSC
October 2018	Final study report submitted to FDA

T. AMENDMENT – REVISED: CLARIFICATION OF LENGTH OF SUBJECT PARTICIPATION

- **We removed the last sentence of the original version of this amendment. The inclusion of this sentence was an accidental oversight of a decision from when the protocol committee was considering an extension to the SUPeR study (i.e. e-SUPeR). The intent of this decision was to help facilitate a clear separation of the studies and assist with enrollment.**

- **The last sentence of the original version of this amendment has been replaced with an explicit statement regarding when participants should be unmasked.**

Background

The primary aim of SUPeR was to determine whether treatment success in women with symptomatic uterovaginal prolapse undergoing transvaginal mesh augmented hysteropexy differs in women undergoing vaginal hysterectomy and native tissue cuff suspension at time points through 3 years. The study was designed with a survival analysis approach with 36 month follow-up after last enrollment with an expected 2 year enrollment period. SUPeR randomization began in April 2013, enrollment ended in October 2014, and the last surgery (randomization) was performed in January 2015. Because there is a 6 week window for the final visit, we will have 3 year data on all continuing participants by March 2018. By April 2018, subjects in SUPeR will have been followed every 6 months for 3 to 5 years. The primary outcome should be available by April 2018.

As the protocol states, one of the advantages of the survival analysis approach is that the study continues to accumulate information on individuals enrolled early in the study as they have events beyond the three-year time frame. The protocol states, “As such, the survival approach with multiple looks will allow the analysis of the primary outcome of overall risk of treatment failure for the study to be completed and results published, while still collecting information on longer-term outcomes.” This clearly implies the intention of continuing to collect data for all subjects every 6 months for 5 years. Indeed, the schedule of measures, the study budget and the informed consent to patients emphasized every 6 month visits up to 5 years (60 months). All subjects were consented to participate in SUPeR and undergo visits every 6 months for up to 5 years (60 months). The 30, 42, and 54 month visits are abbreviated visits that collect data for the primary and major secondary outcomes (POPQ, mesh exam, PFDI-Q3, and AE survey).

Some investigators had interpreted that the study ends when the last patient reaches the 3 year follow-up. There is ambiguity in the protocol and in the compensation section of the consent form that suggests that not everyone might complete 60 months of visits.

Purpose

The purpose of this amendment is to clarify the length of subject participation.

- **We clarify that all subjects should be followed every 6 months for 60 months (5 years).**

In support of this clarification we note:

1. The schedule of measures, the study budget and the informed consent to patients emphasized every 6 month visits up to 5 years (60 months). Patients were consented and agreed to every 6 month visits for up to 60 months (5 years)

2. We believe that this amendment does not require reconsenting subjects at most sites because subjects were consented to every 6 month visits for up to 60 months. However, this decision is made by each local IRB.

All participants should be unmasked by a study coordinator at the completion of their 60-month study visit.

U. AMENDMENT: EXTENSION OF THE STUDY OF UTERINE PROLAPSE PROCEDURES-RANDOMIZED TRIAL (SUPeR) STUDY FOR LONG-TERM FOLLOW-UP TO 10 YEARS (E-SUPeR)

Background

The primary aim of SUPeR was to determine whether treatment success in women with symptomatic uterovaginal prolapse undergoing transvaginal mesh augmented hysteropexy differs in women undergoing vaginal hysterectomy and native tissue cuff suspension at time points through 3 years. The study was designed with a survival analysis approach with 36 month follow-up after last enrollment with an expected 2 year enrollment period. SUPeR randomization began in April 2013, enrollment ended in October 2014, and the last surgery (randomization) was performed in January 2015. All subjects reached 3 year follow-up in March 2018. Retention in this time period was excellent; three year primary outcome data was available for 96% of the participants. Some participants have reached the 5 year follow-up time point and have been unmasked.

What has become apparent with this excellent follow-up is that the SUPeR cohort represents a unique opportunity to understand the longer term efficacy and safety outcomes of a native tissue repair and a mesh hysteropexy. There are no studies in the literature with such outstanding long-term follow-up over an extended period of time. The current 96% retention rate underscores how readily participants accept the evaluations that have been performed in this study.

Proposed Extension of Study

This amendment proposes to continue to follow the subjects in this study who have not undergone reoperation for prolapse until reoperation for prolapse is reported, 10 years of follow-up is completed, or until participant retention in this study falls below 60%. To decrease subject burden, the frequency of study visits will be reduced from every 6 months to annually from the date of surgery. A reduction of select secondary patient reported outcome measures that are unlikely to provide interesting data during this 5-10 year time period is proposed.

The annual follow-up visits for year 6 could begin as early as April 2019 when our first subject reaches the 6 year mark. The table below represents the abbreviated outcome measures that will be collected at each annual visit.

Measure	6 years	7 years	8 years	9 years	10 years
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

Measure	6 years	7 years	8 years	9 years	10 years
PFIQ	X	X	X	X	X
PGI-I	X	X	X	X	X
ISI	X	X	X	X	X
PISQ-IR	X	X	X	X	X

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
- BIS
- SF-12

Limited (Virtual) Participation Option

The following subjects can be offered the opportunity to consent to limited study participation: participants who discontinued, withdrew consent, were withdrawn by investigator, or were lost to follow-up during the initial 5-year SUPeR study, and subjects who initially declined to enroll in E-SUPeR. All of the subjects described 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.)

The table below represents the outcome measures that will be collected at each annual visit under the limited participation option.

Measure	6 years	7 years	8 years	9 years	10 years
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
ISI	X	X	X	X	X
PISQ-IR	X	X	X	X	X

Adverse Event Collection and Reporting

The E-SUPeR study is an observational extension of the original SUPeR protocol and does not involve a treatment intervention. A primary goal of E-SUPeR is to ascertain the long-term failure rates associated with vaginal hysterectomy plus uterosacral ligament suspension and mesh hysteropexy. 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 collagen) 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.

Outcomes that are not likely related to native tissue repair or mesh hysteropexy (i.e., non-urologic/non-colorectal/non-gynecologic diagnoses, procedures and hospitalizations) will not be collected. Outcomes classified as serious adverse events (SAEs), defined as all deaths and SAEs that are considered related to the index surgery of SUPeR or the pelvis, will be reported to the Medical Safety Monitor, DSMB, site IRB (per local IRB requirements), and NICHDIRB in an expedited manner. By definition, as E-SUPeR starts five years after the randomization for the index surgery of SUPeR, fatalities will most likely not be related to native tissue repair or mesh hysteropexy, but all fatalities regardless of relationship to the study surgeries will be collected for E-SUPeR.

Sample Size Estimate

The available cohort includes a total of N = 156 subjects after excluding those initially ineligible for the SUPeR study, deaths, and those who have had a second surgery secondary to index surgery failure during the 5year SUPeR study. Any participants who undergo reoperation for prolapse between completing the 5-year SUPeR study and being assessed for E-SUPeR will be considered eligible for the extension. Limited data regarding the second surgery will be collected and then the subject's participation will end immediately thereafter. It is anticipated that the number of participants in follow up will be reduced by approximately 5% per year due to either withdrawal or reoperation for prolapse.

Feasibility and Statistical Analysis

If overall participant retention 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.

Once the study is completed, differences between the treatment groups in long-term surgical success and other outcomes will be evaluated using statistical methods consistent with the analyses performed at 3 and 5 years.