Registry Protocol–**Research Registry (PFDR-R)**

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Table of Contents

List of Abbreviations **4**

1. Background **5**

2. Rationale **7**

3. Objectives **8**

4. Registry Design **9**
4.1 Registry Description 9
4.2 Levels of Participation 9
4.3 Registry Population 11
4.3.1 Inclusion Criteria *11*
4.3.2 Exclusion Criteria *11*
4.3.3 Site and Provider Enrollment *12*
4.3.4 Patient Enrollment *12*
4.3.5 Patient Withdrawal *12*
4.3.6 Registry or Study Discontinuation *12*
4.4 Definitions and Outcome Measures 13
4.4.1 Pelvic Organ Prolapse Compartments *13*
4.4.2 Pelvic Organ Prolapse Treatments *13*
4.4.3 Primary Effectiveness Outcome Measures *15*
4.4.4 Secondary Effectiveness and Quality of Life Outcome Measures *16*
4.4.5 Primary Safety Outcome Measures *17*
4.5 Data Collection 17
4.5.1 Surgeon and Registry Site Information *17*
4.5.2 Patient Data *17*

5. Statistical Methods **20**
5.1 Overview 20
5.2 Missing Data 21
5.3 Data Reporting 21

6. Registry Conduct **21**
6.1 Governance 21
6.2 Data Entry/Electronic Data Capture 22
6.3 File Retention and Archiving 22
6.4 Quality Assurance 23
6.5 Data Management 23
6.6 Protocol Amendments 23
6.7 Requests for Ancillary Data Analyses 23
6.8 Publication Policy 24

7. Safety Reporting **24**
7.1 Definitions 24

7.2 Reporting to the FDA 25

8. Ethical and Regulatory Considerations 25
8.1 Guiding Principles 25
8.2 Risks and Benefits of Patient Participation 25
8.3 Patient Information and Informed Consent 25
8.4 Patient Confidentiality 26
8.5 Institutional Review Board 26
8.6 Separation of Industry Sponsored Data 27

9. References 27

Appendix Adverse Event (AE) and Related Clinically Important Event Definitions* 30

List of Abbreviations

ACOG	American Congress of Obstetrics and Gynecology
AE	Adverse event
AUA	American Urologic Association
AUGS	American Urogynecologic Society
BMI	Body mass index
CFR	Code of Federal Regulations
CMS	Centers for Medicaid and Medicare Services
CRF	Case report form
eCRF	Electronic case report form
EDC	Electronic data capture
HRT	Hormone replacement therapy
ICIQ-UI SF	International Consultation on Incontinence Questionnaire- Urinary Incontinence – Short Form
ICU	Intensive Care Unit
FDA	U.S. Food and Drug Administration
FI	Fecal incontinence
FPMRS	Female Pelvic Medicine and Reconstructive Surgery
HIPAA	Health Insurance Portability and Accountability Act
MAUDE	Manufacturer and User Device Experience database (FDA)
MDR	Medical device report
MMK	Marshall Marchetti Krantz procedure
OR	Operating room
PFD	Pelvic floor disorder
PFDR	Pelvic Floor Disorders Registry
PFDR- IS	Pelvic Floor Disorders Registry -
PFDR-R	PFDR - Research
PFDI-20	Pelvic Floor Distress Inventory – 20 Item Short Form
PFIQ-7	Pelvic Floor Impact Questionnaire – 7 Item Short Form
PGI-I	Patient Global Impression of Improvement
PHN	Public health notification
PISQ-12	Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire – 12 Item Short Form
PME	Pelvic muscle exercise
POP	Pelvic organ prolapse
POP-Q	Pelvic Organ Prolapse Quantification system
PQRS	Physician Quality and Reporting Systems
PRO	Patient-reported outcome
RCT	Randomized controlled trial
RSC	Registry Steering Committee
QoL	Quality of life
SAP	Statistical analysis plan
SUI	Stress urinary incontinence
SUFU	Society for Urodynamics and Female Pelvic Medicine and Urogenital Reconstruction
UDS	Urodynamics
UI	Urinary incontinence

US	United States
WHRA	Women's Health Registry Alliance
VTE	Venous thromboembolism

1. Background

Pelvic Floor Disorders (PFD) include a broad array of interrelated clinical conditions that includes urinary incontinence (UI), pelvic organ prolapse (POP), fecal incontinence (FI), sensory and emptying abnormalities of the lower urinary tract and defecatory dysfunction. Nearly one quarter of all women and more than one-third of older women report symptoms of at least one PFD, according to national population-based estimates [Nygaard 2008]. Approximately one in five women will undergo surgery for UI and/or POP by age 80 with 30% of those women undergoing two or more surgical procedures [Wu, 2014,Olsen 1997]. Economic analyses estimate that the total cost of UI alone is up to $19.5 billion (in year 2000 dollars) annually [Hu 2004]. Beyond the economic costs and general healthcare burden, PFD result in significant psychosocial costs and can have a profound impact on an individual's quality of life [Landefeld 2008]. The prevalence of PFD increases with age and it is estimated that the growth in demand for services to care for women with PFD will increase at twice the rate of growth of the population over the next 30 years [Luber 2001].

POP is the downward descent of the female pelvic organs (vagina, uterus, bladder and/or rectum) into or through the vagina. Loss of vaginal or uterine support in women presenting for routine gynecology care is seen in up to 43%-76% of women, with 3%-6% of those with descent beyond the hymen and approximately 3% of women developing symptomatic vaginal bulging [Nygaard 2008, Ellerkmann 2001, Swift 2000]. Women with POP often have other concurrent PFDs. Ellkermann et al found that in 237 women evaluated for POP 73% reported urinary incontinence, 86% reported urinary urgency and/or frequency, 34-62% reported voiding dysfunction and 31% complained of FI.

POP is a prevalent condition that can substantially affect a woman's daily living and quality of life. It can affect a woman's body image, sexual function and family relationships. Treatment options for women with prolapse range from observation, the use of a pessary or a surgical repair. A woman's lifetime risk of surgery for POP is approximately 12.6% [Wu 2014]. Over 300,000 prolapse surgeries are performed annually in the United States (US). POP accounts for approximately 15%-18% of hysterectomies in the US and uterovaginal prolapse is the most common indication for hysterectomy in postmenopausal women [Jacobson 2006, Whiteman 2008]. Of those who receive surgery, an estimated 13% will require a repeat operation within 5 years, and as many as 29% will undergo another surgery for genital prolapse or a related condition at some point during their life [Olsen 1997, Clark 2003]. Prolapse of the anterior vaginal wall, or cystocele, is the most common form of POP and the most likely to recur after surgery [Clark 2003].

The treatment of POP is complex and often involves treating multiple concurrent disorders of bowel, bladder and sexual function in addition to correcting the prolapse of the pelvic organs. Options for treatment include observation, pessary use and surgery.

Non-Surgical Treatments

Other than observation, pessary use is the principal non-surgical intervention available for women with POP. Pessary devices are inserted into the vagina to reduce prolapsed tissue inside the vagina, to provide support to related pelvic structures, and to relieve pressure on the bladder and bowel in order to avert or delay the need for surgery [Wilson 2005, Adams 2004].

Surgical Treatments

A variety of surgeries exist for the surgical correction of POP including transvaginal native-tissue (non-mesh) repairs, transvaginal mesh repairs and abdominal repairs (sacrocolpopexy) using mesh or native tissue which can be performed via laparotomy, or via laparoscopy with or without robotic assistance. Reinforcement of vaginal repairs with synthetic mesh has been widely employed in the hope of improving the effectiveness and durability of vaginal prolapse repairs, with almost one-quarter of all prolapse repairs currently involving the placement of transvaginal mesh. Surgical mesh materials used to correct POP can be divided into four general categories: (a) non-absorbable synthetic (e.g., polypropylene or polyester); (b) absorbable synthetic [e.g., poly (lactic-co-glycolic acid) or poly (caprolactone)]; (c) biologic (e.g., acellular collagen derived from bovine or porcine sources); or, composite (i.e., a combination of any of the previous three categories). There is currently no consensus regarding which surgical approach is superior and each has its own risk-benefit profile. Most Female Pelvic Medicine and Reconstructive Surgery (FPMRS) specialists incorporate multiple different approaches in their practice, tailoring the specific technique to the individual patient and her unique characteristics and preferences.

A 2013 Cochrane review evaluated 5,954 participants in 56 trials of different surgical procedures for POP made several conclusions including: 1) abdominal sacrocolpopexy had lower recurrent vault prolapse rates than native tissue repair using sacrospinous colpopexy but this was balanced against longer time to return to activities of daily life and higher complications; and 2) that native tissue repair was associated with more anterior compartment failures than transvaginal mesh grafts (overlay: RR 2.14 (95% CI 1.23-3.74; trocar guided kits RR 3.15, 95% CI 2.50 to 3.96) [Maher, 2013]; 3) awareness of prolapse was also higher after the anterior repair as compared to polypropylene mesh repair (28% versus 18%, RR 1.57, 95% CI 1.18 to 2.07). However, the reoperation rate for prolapse was similar at 14/459 (3%) after the native tissue repair compared to 6/470 (1.3%) (RR 2.18, 95% CI 0.93 to 5.10) after the anterior polypropylene mesh repair and no differences in quality of life data or de novo dyspareunia were identified. Blood loss (MD 64 ml, 95% CI 48 to 81), operating time (MD 19 min, 95% CI 16 to 21), recurrences in apical or posterior compartment (RR 1.9, 95% CI 1.0 to 3.4) and de novo stress urinary incontinence (RR 1.8, 95% CI 1.0 to 3.1) were significantly higher with transobturator meshes than for native tissue anterior repair. Mesh erosions were reported in 11.4% (64/563), with surgical interventions being performed in 6.8% (32/470). Data from three trials compared native tissue repairs with a variety of total, anterior, or posterior polypropylene kit meshes for vaginal prolapse in multiple compartments. While no difference in awareness of prolapse was able to be identified between the groups (RR 1.3, 95% CI 0.6 to 1.7) the recurrence rate on examination was higher in the native tissue repair group compared to the transvaginal polypropylene mesh group (RR 2.0, 95% CI 1.3 to 3.1). The mesh erosion rate was 35/194 (18%), and 18/194 (9%) underwent surgical correction for mesh erosion. The reoperation rate after transvaginal polypropylene mesh repair of 22/194 (11%) was higher than after the native tissue repair (7/189, 3.7%) (RR 3.1, 95% CI 1.3 to 7.3) Another systematic review analyzed the complications and reoperation rates for surgical procedures specifically performed to correct apical POP: native tissue vaginal repairs, sacrocolpopexy and vaginal

mesh kits. Another systematic review analyzed the complications and reoperation rates for surgical procedures specifically performed to correct apical POP: native tissue vaginal repairs, sacrocolpopexy and vaginal mesh kits. In this review, the rate of reoperation to correct recurrent prolapse was lowest in those who received transvaginal mesh; however, reoperations for complications as well as the total reoperation rate was highest for vaginal mesh kits compared with vaginal native tissue and abdominal repairs, despite shorter overall follow-up [Diwadkar, 2009]. In a recent randomized controlled trial (RCT) of 389 women assigned to anterior mesh or anterior colporrhaphy, higher success rates based on a composite outcome of subjective absence of a bulge and anatomic stage 0 or stage I prolapse, higher success rates were seen with anterior mesh (60.8%) compared with native tissue anterior colporrhaphy (34.5%) at 1 year. [Altman 2011]. Rates of intraoperative bladder injury and hemorrhage were higher in the mesh group, and *de novo* stress incontinence also was higher (12.3% versus 6.3%). However, surgical re-intervention for mesh exposure was relatively low at 3.2%.

2. Rationale

For both non-surgical and surgical treatment options for POP there is very little systematically collected data upon which to make informed clinical decisions. In the 2009 Cochrane review of pessary use, no eligible randomized trials of pessary use in women with POP were identified [Adams 2004]. Although there is evidence that the use of pessaries in the treatment of POP is effective in alleviating symptoms, the discontinuation rate is high in many series (23%-50% in the first year) [Lamers 2011]. Moreover, the follow-up in many published papers is short, the use of validated symptoms and quality of life questionnaires is limited, and comparison with surgical treatment of POP is rare. [Lamers 2011]. Despite these limitations, 86% of gynecologists and 98% of urogynecologists use pessaries in their practice and it is considered first-line treatment for POP in many patients [Jelovsek 2007].

The existing literature evaluating the surgical treatments for POP also has several significant limitations. Many studies are poorly designed, are underpowered, use incompletely documented inclusion/exclusion criteria, fail to account for various lengths of patient follow-up, and few studies follow patients beyond two years.[FDA July 2011] Moreover, many studies use strict anatomic efficacy outcomes to define treatment success that may not be clinically relevant [Barber 2009, Chmielewski 2011]. Advancing evidence on the epidemiology of POP and the relationship between vaginal support and symptom development has led to recommendations that the definition of treatment success after POP surgery consist of a composite outcome that includes absence of vaginal bulge symptoms, absence of vaginal descent beyond the hymen and the absence of retreatment [Barber 2009]. Additionally, comparative effectiveness and safety data for many surgical techniques that have gained significant popularity in the past few years including sacrocolpopexy using laparoscopic and robotic approaches and single-incision (trocarless) transvaginal mesh kits are lacking.

In October 2008, the FDA issued a Public Health Notification (PHN) to inform clinicians and patients of adverse events (AEs) related to urogynecologic use of surgical mesh and to provide recommendations on how to mitigate risks and counsel patients. Following the PHN, the FDA continued to monitor the outcomes of urogynecologic use of surgical mesh. A search of the FDA's Manufacturer and User Device Experience (MAUDE) databases from January 2008 – December 2010 identified 1503 medical device reports (MDRs) for urogynecologic surgical meshes associated with POP repair. On 13 July 2011, the

FDA provided an updated PHN on urogynecologic surgical mesh and reported that the complications of mesh used transvaginally are not rare. The FDA conducted a systematic review of the published scientific literature from 1996 to 2011 to evaluate the safety and effectiveness of vaginal mesh used for the repair of prolapse. Key conclusions of the FDA's review were that (1) serious adverse events are NOT rare, contrary to what was stated in the 2008 PHN and (2) transvaginally placed mesh in POP repair does not conclusively improve clinical outcomes over traditional non-mesh repair. In September 2011, the FDA convened a meeting of the Obstetrics-Gynecology Devices Panel of the Medical Devices Advisory Committee to discuss the safety and effectiveness of transvaginal placement of mesh for POP and stress urinary incontinence (SUI). Following the Panel's recommendation, on 3 January 2012 the FDA ordered manufacturers of transvaginal mesh products for POP to conduct postmarketing surveillance under Section 522 of the Federal Food, Drug and Cosmetic Act (i.e., "522 order"). In a December 2011, Committee Opinion on Vaginal Placement of Synthetic Mesh for POP, the American Urogynecologic Society (AUGS) and the American College of Obstetricians and Gynecologists (ACOG) issued a number of recommendations including strong support for continued audit and review of outcomes, as well as the development of a registry for surveillance for all current and future urogynecologic mesh implants.

To support these recommendations, AUGS is initiating a national registry [the Pelvic Floor Disorders Registry (PFDR)] in order to track surgeon volume, patient baseline measures, both short-term and long-term objective (anatomic) and subjective (prolapse symptoms and sexual function) effectiveness, quality of life and safety outcomes. The PFDR is intended to track patients who have undergone procedures using mesh (either vaginal or abdominal) as well as vaginal and abdominal non- mesh ("traditional") repairs and nonsurgical management with pessaries, in order to evaluate both mesh and non-mesh repairs.

This protocol addresses the Research Registry (PFDR-R), which will include clinical data and patient-reported outcomes for research and quality improvement purposes.

3. Objectives

The PFDR is a national registry for providers who care for patients with PFDs to provide much needed information about the comparative effectiveness, quality of life and safety associated with various surgical and nonsurgical treatments and ultimately to improve the quality of care for women with these conditions. Broadly, the registry aims to provide evidence for best medical practices for the advancement of public health with respect to treatment modalities available for PFDs, and specifically POP, by (1) collecting, storing and analyzing comprehensive clinical data from a broadly representative patient population; (2) establishing common data elements and quality metrics in cooperation with the Women's Health Registry Alliance and (3) providing a framework for stakeholders to conduct research to improve knowledge in the field. The PFDR is divided into two distinct but related registries in order to meet the many goals noted previously: the Research Registry (PFDR-R) and the Industry Sponsored Registry (PFDR – IS). This protocol describes the Research Registry.

The primary objectives of the Research Registry (PFDR-R) are to:

- Provide a powerful quality improvement tool that will provide feedback to surgeons and their practices about the care they provide.

- Allow healthcare providers to track surgeon volume, patient outcomes, and quality measures and maintenance of certification (MOC) requirements
- Evaluate the effectiveness, quality of life and safety associated with surgical options (transvaginal/transabdominal native tissue repair, transvaginal mesh repair and sacrocolpopexy) for POP
- Assess the effectiveness, quality of life and safety associated with non-surgical management (pessary) for POP
- Provide a framework for clinical studies to be conducted within the registry

The secondary objectives of the registry include to:

- Identify modifiable and non-modifiable risk factors associated with complications and reduced effectiveness of PFD treatments
- Capture comprehensive data that includes those elements required by the FDA's requirement for postmarketing surveillance of transvaginal mesh use for POP
- Function as resource for additional PFD research, whereby stakeholders and participants may propose and conduct analyses of registry data (as approved by PFD Research Registry Committee)

In the future, the registry objectives may be expanded to include evaluation of treatment for SUI without concurrent POP and potentially other PFDs.

4. Registry Design

4.1 Registry Description

The PFDR is a national, multi-centered prospective cohort study of patients undergoing treatment for POP (with or without other PFDs) to evaluate the effectiveness, quality of life and safety associated with both surgical therapy (transvaginal/transabdominal native tissue repair, transvaginal mesh repair and sacrocolpopexy) and non-surgical management (pessary). The PFDR Research Registry is designed to collect both provider and patient reported outcomes for both quality and research purposes through broad participation from specialists and generalists performing surgery for prolapse.

In addition to AUGS, stakeholders for the overall PFDR include, but are not limited to, ACOG, the Society for Urodynamics and Female Pelvic Medicine and Urogenital Reconstruction (SUFU), American Urologic Association (AUA), Women's Health Registry Alliance, FDA, *Eunice Kennedy Schriver* National Institute for Childhood Health and Human Development (NICHD), participating providers and the medical device industry.

4.2 Levels of Participation

In order to meet its objectives, the PFDR has two levels of participation for providers participating in this project. The levels of registry participation are described in Table 1. Participation in the Research (PFDR-R) Registry will be voluntary; sponsorship by a medical device company or other commercial interest is strictly prohibited. Data from industry

sponsored studies including the 522 postmarketing surveillance studies will be captured exclusively in the Industry Sponsored Research Registry (PFDR-IR).

Table 1. PFD Registry Levels of Site Participation

Research Registry (PFDR-R)	**Description:** A more comprehensive set of variables to address effectiveness, quality of life associated with both surgical and non-surgical treatment of POP that, in addition to the variables in the Universal Minimum Data Set, includes additional symptom and quality of
	Attributes: • Includes data elements including condition-specific symptom and quality of life measures • Includes patient reported variables that may be collected from patients who may not be seen back in clinic • Includes similar data elements required in the FDA mandated post-marketing surveillance studies, to allow for comparisons between patients included in these studies and the overall registry population • Includes data collection on patients receiving non-surgical (pessary) treatment for POP
Industry Sponsored Research Registry (PFDR-IS)	**Description:** A mechanism to allow stakeholders, and in particular the medical device industry, to sponsor and perform unique cohort studies within the framework of the registry.
	Attributes: • Includes all data from the Quality & Research Registry • May also include additional unique data elements as specified in a study specific protocol. • This level of data collection will be used for industry sponsored studies, including those necessary to fulfill post-market surveillance • (522) studies for transvaginal mesh.

4.3 Registry Population – PFDR-R

Provider/site and patient participation in the PFDR is voluntary. The goal of the registry is to provide representative data from providers of surgical and non-surgical treatment for PFD. This may include, but is not limited to, gynecologists, urologists, and FPMRS specialists including urogynecologists and female urologists.

The population for the PFDR-R will include adult female patients receiving surgical and non-surgical treatment for PFD and will initially focus on following patients for up to 36 months after initiating non-surgical and surgical treatments for POP. The length of follow-up may be extended during the course of the registry. In order to capture the safety and effectiveness of the full spectrum of POP treatments provided in a widely generalizable population the inclusion criteria are broadly defined. These inclusion criteria may be expanded at a later date to include patients receiving treatment for SUI and other PFDs.

In order to understand the base population from which the registry population is sampled, with the assistance of operating room logs or other administrative databases, providers participating will be asked to provide a count of those patients presenting for treatment of POP (i.e., patients eligible for the registry) that did not wish to participate in the registry, characterizing them with respect to vaginal native tissue or mesh augmented repair, abdominal repair or non-surgical treatment. No other information will be collected on these patients.

4.3.1 Inclusion Criteria

In order to be enrolled in the PFDR-R, patients must meet the following criteria:

- Female
- Age ≥ 18 years or ≥ 19 in Alabama, Nebraska or ≥ 20 Puerto Rico. Minors will not qualify for participation.
- Newly electing surgical or non-surgical (pessary) management of POP in one or more compartments
- Willing to participate in 36 months of longitudinal follow-up and able to provide written informed consent.Willing to provide an email address and complete questionnaires on-line, either in clinic or elsewhere when they have access to the internet. If unwilling or unable to complete on-line questionnaires, willing to complete paper questionnaires in the clinic or to complete and return paper questionnaires via mail.

4.3.2 Exclusion Criteria

Patients meeting ANY of the following criteria are not eligible for participation in PFDR-R:

- Currently pregnant at enrollment
- Physically or mentally unable, in the opinion of the provider, to participate in up to 36 months of follow-up
- Desires non-surgical management of POP other than pessary (e.g. pelvic muscle exercises, observation only)

In the future, the registry may be expanded to include women undergoing treatment for stress urinary incontinence without concurrent POP and perhaps women with other PFDs.

4.3.3 Site and Provider Enrollment

Healthcare providers of women with PFD, including gynecologists, urologists, and FPRMS specialists including urogynecologists and female urologists, in both academic and private practice settings, will be eligible to participate in the PFDR. Sites and providers will be further qualified for participation based on their ability to provide data using the electronic data collection (EDC) system and sufficient personnel to support registry activities.

4.3.4 Patient Enrollment

Patients will be enrolled prospectively from participating PFDR sites prior to initiation of treatment. Surgeons participating in the Industry Sponsored Research Registry may also enroll patients who do not qualify for or wish to participate in such studies into the Research Database of the registry depending upon their level of interest. All patients whose data will be included in the Research Registry will complete written informed consent prior to enrollment and any data collection.

Eligible patients will be enrolled in the registry at the time of decision for planned surgical or non-surgical treatment for POP during a routine clinic visit. No clinic visits are required as part of participation in this registry beyond those that are part of routine clinical care. All assessments for sites participating in the Research Registry are intended to be performed at the time of a routine clinical encounter, by an electronic patient reporting of outcomes or by referencing the medical record.

Patients who enroll in PFDR-R with a PFDR site/surgeon and then transfer their care to another site/surgeon participating in the registry may continue in full participation with the registry. The data contained within those forms will be linked, such that the clinical course of events is accurately reported. Similarly, once a patient is enrolled in PFDR-R, she will continue to receive notifications for direct reporting of data to the registry, regardless of her clinical follow-up with a registry host site/surgeon.

4.3.5 Patient Withdrawal

Patients may withdraw consent and discontinue participation in the registry at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the registry follow-up period, any known reason for withdrawal should be documented in the database. All information already collected as part of the registry will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

4.3.6 Registry or Study Discontinuation

If the registry (or specific studies conducted within the registry) is discontinued, data collected prior to discontinuation would remain within the registry for inclusion in future analyses.

4.4 Definitions and Outcome Measures

4.4.1 Pelvic Organ Prolapse Compartments

Enrolled patients will be classified as having POP in the anterior, posterior and/or apical vaginal compartments based upon the anatomic criteria shown in Table 2. These classifications are not mutually exclusive and it is expected that many patients in the registry will have POP in more than one compartment.

Table 2. Prolapse Compartment Anatomic Criteria

Segment	Description	POP-Q Criteria*
Anterior	Prolapse of the anterior vaginal wall beyond the hymen with maximum Valsalva	Point Ba > 0
Posterior	Prolapse of the posterior vaginal wall beyond the hymen with maximum Valsalva	Point Bp > 0
Apical	Prolapse of the cervix or vaginal cuff more than half way down the length of the vagina with maximum Valsalva	Point C > 0 (single compartment) Point C ≥ -1/2 TVL (multi-compartment)

POP-Q: Pelvic Organ Prolapse Quantification system [Bump 1996], TVL: total vaginal length
* POPQ required for the Quality & Research and Industry Sponsored Research Registries

4.4.2 Pelvic Organ Prolapse Treatments

All POP treatments will be captured in the registry. For the purposes of sub-grouping primary treatment types for analysis, the categorizations for treatments are provided in Table 3.

Table 3. Initial POP Treatment Modality Definitions

Non-surgical Management of POP
Includes patients initiating treatment of POP with a vaginal pessary. **NOTE**: Other potential non-surgical treatments for POP including observation and pelvic muscle exercises are not currently eligible for enrollment in the registry
Surgical Management of POP
Includes a variety of surgeries for correction of POP in each vaginal segment.

Transvaginal Native Tissue Repair	• Transvaginal surgical repairs of POP that provide vaginal support using the patient's native tissue and sutures without augmentation by surgical mesh materials including biologic, absorbable or non-absorbable synthetic graft materials. • Native tissue repair for prolapse of the anterior vaginal segment includes anterior colporrhaphy and paravaginal repair. • Native tissue repair technique for prolapse of the posterior vaginal segment is posterior colporrhaphy. • Transvaginal native tissue suspensions of the vaginal apex include both extraperitoneal suspensions (sacrospinous suspension and iliococcygeus suspension) and intraperitoneal suspensions (uterosacral ligament suspension and McCall's culdoplasty and its modifications). • Note: Patients who receive concomitant surgical mesh for treatment of SUI (mid-urethral sling) are not excluded from this category.
Transvaginal Mesh Repair	• Surgical repairs of POP using surgical mesh (absorbable and non-absorbable synthetic, biologic, and composite grafts) placed through a transvaginal incision to augment or support the pelvic organs. • Transvaginal Mesh Repairs can support the anterior, posterior or apical segments alone or in combination. • Commercially marketed transvaginal mesh products can broadly be classified into *free grafts* in which the material consists of only the graft material that is sutured into place by the surgeon and *mesh kits* in which consists of the graft material with an accompanying delivery system for securing or placing the graft. Mesh kits may be further classified as trocar-based and non-trocar based.
Sacrocolpopexy	• Surgical procedure performed transabdominally via laparotomy or laparoscopically with or without robotic assistance whereby the upper vagina and/or cervix is attached to the sacrum using one or more strips of surgical mesh. • Used primarily to correct apical prolapse but can also be used to correct anterior or posterior defects depending upon the points of attachment and length of the surgical mesh.
Obliterative repairs	• Total colpocleisis • LeFort's partial colpocleisis • Corrects pelvic organ prolapse by moving pelvic viscera back into the pelvis and closing off the vaginal canal either partly or totally.
Other PFD Treatments	
Concurrent hysterectomy and anti-incontinence procedures performed in conjunction with POP surgery will also be captured.	• Mid-urethral slings (retropubic, transobturator, and single incision [mini-slings]) • Retropubic colposuspensions (Burch, MMK) • Bladder neck slings, autologous (rectus fascia or fascia lata), allograft (cadaveric) or xenograft • Hysterectomy with or without oophorectomy

Surgical procedures performed, by route (transvaginal or abdominal) is provided in Table 4.

Table 4. Surgical procedures for POP by route

Segment	Surgical Approach	Route	
		Transvaginal	**Abdominal***
Anterior	Native Tissue	Anterior colporrhaphy Paravaginal repair	Paravaginal repair
	Mesh augmented	Free graft Mesh Kit#	Sacrocolpopexy
Posterior	Native Tissue	Posterior colporrhaphy Perineorrhaphy	n/a
	Mesh augmented	Free graft Mesh Kit#	Sacrocolpopexy
Apical	Native Tissue	Vaginal Vault Suspension: • Uterosacral • Sacrospinous • Iliococcygeus Enterocele repair	Abdominal Vaginal Vault Suspension: • Uterosacral Enterocele repair
	Mesh augmented	Free graft Mesh Kit#	Sacrocolpopexy
Obliterative (all compartments)	Native Tissue	Colpocleisis	n/a

***** includes procedures performed via laparotomy and laparoscopy with or without robotic assistance.
# specific mesh kits may be designed to address more than one segment (e.g. anterior/apical; posterior/apical; total (anterior, posterior, apical))

4.4.3 Primary Effectiveness Outcome Measures

The following definitions will be utilized to characterize treatment effectiveness:

- **Subjective success:** The criteria for subjective success after surgical or non-surgical treatment will be considered met if the patient denies symptoms of vaginal bulging as indicated by a negative response (”No”) to Pelvic Floor Distress Inventory (PFDI-20) question #3 “Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?” [Barber 2005]
- **Anatomic success:** The criteria for anatomic success after surgical treatment of POP will be considered met if there is no vaginal or uterine descent beyond the hymen on pelvic examination with the patient performing maximal Valsalva. Anatomic success will be reported by segment and overall (all segments) using the following criteria:
    - Anterior Segment : No anterior prolapse beyond the hymen or POPQ point Ba ≤ 0
    - Posterior Segment : No posterior prolapse beyond the hymen or POPQ point Bp ≤ 0
    - Apical Segment : No prolapse of the cervix /vaginal apex beyond the hymen or POPQ point C ≤ 0
    - Overall: No prolapse of any segment beyond the hymen or POPQ point Ba, Bp, and C each ≤ 0

- **No retreatment for POP [in the treated segment(s) and overall]**: The criteria for this no retreatment will be considered met if the patient has not received additional surgical treatment for POP or used a pessary since the index surgery. No retreatment will be reported for the treated segment and overall using the following criteria:
    - No retreatment (treated segment): No additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery.
    - No retreatment (overall): No additional surgical treatment for POP in any segment or use of a pessary since the index surgery.

The primary effectiveness endpoint for patients undergoing surgical treatment for POP is a dichotomous outcome: surgical treatment "success" or "failure." Subjects will be considered a surgical success for this composite outcome if each of the three criteria is met using the definitions outlined above [Barber 2009]:

- Subjective success
- Anatomic success
- No retreatment for POP

The primary effectiveness endpoint for patients who elect pessary management will be a dichotomous outcome: non-surgical treatment "success" or "failure." Patients will be considered a non-surgical treatment success if they meet both of the following criteria:

- Subjective success
- No surgical treatment for POP since initial pessary placement

Note: Patients meeting criteria for Subjective success prior to initiating pessary treatment will not be included in assessments of this endpoint.

4.4.4 Secondary Effectiveness and Quality of Life Outcome Measures

The following secondary effectiveness outcome measures will be used to evaluate treatments for POP:

- Anatomic success for each vaginal segment involved (anterior, posterior and apical)
- Time to anatomic prolapse recurrence (time to failure)
- Time to symptomatic prolapse recurrence (time to failure)
- Changes in urinary function (PFDI-20 Questions #16-18)
- Changes in patient-reported sexual activity/dyspareunia
- Patient global impression of improvement (PGI-I)
    - Prolapse [Srikrishna 2010]
    - Urinary Function [Yalcin 2003]
- Rate of surgical intervention
    - Surgical intervention for complications
    - Surgical intervention for stress urinary incontinence (includes periurethral bulking injections)

Other effectiveness and QOL outcome measures utilized in the Research Registry (PFDR-R) may include all of the outcomes above, as well as those listed below:

- Anatomic success for each vaginal segment (anterior, posterior, and apical) assessed by their corresponding POP-Q point (Ba, Bp, C) measured as continuous variables.
- Pelvic pain/discomfort in the lower abdomen, vagina and vulva
- Changes in condition-specific quality of life
    - PFDI-20 [Barber 2005]
    - Pelvic Floor Impact Questionnaire (PFIQ-7) [Barber 2005]
- Changes in sexual function and measured by the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) [Rogers 2003]
- Changes in urinary function as measured by the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF) [Avery 2004]
- Changes in generic QOL: PROMIS Global Health Questionnaire [add reference]

4.4.5 Primary Safety Outcome Measures

The primary safety endpoints for patients undergoing surgical intervention for POP will consist of post-treatment adverse events. Safety outcomes will include the frequency of post-treatment adverse events (AEs), including both intraoperative and postoperative (≤ 12 weeks) AEs, as well as long-term AEs related to the index treatment for those patients managed surgically. AE data will be captured both through provider and patient reporting. A complete list of AEs being assessed and their definitions can be found in Appendix A.

4.5 Data Collection

4.5.1 Surgeon and Registry Site Information

A surgeon characteristics form will be completed by each participating surgeon upon agreement to participateand prior to enrolling patients into the PFDR-R and will be updated annually. This form will constitute commitment on the part of the provider to participate in this registry and will collect the following information:

- Hospital profile(s), including contact information, type (community, university-affiliated, university, military)
- Surgeon profile, including contact information, years of practice, fellowship training Y/N and type, yearly surgical PFD volume, yearly clinical PFD volume and number of years performing PFD treatment (surgical or non-surgical)

4.5.2 Patient Data

Patient data will be collected after informed consent is obtained and prior to initiating treatment (baseline) and post-operatively/post-pessary placement. Postoperative/post-placement assessments will include patient-reported outcome assessments (PRO) obtained via the registry's electronic PRO system (ePRO) at baseline, 2, 6, 12, 18, 24 and 36 months after surgery or pessary placement). For most participants, questionnaires will be administered online. The participant will be emailed a link automatically from the PFDR database after enrollment and then at specified times for follow-up. Each link is unique to that participant and to the

specified visit, so the data automatically populates the database correctly. Participants may elect to complete these questionnaires in the clinic on a tablet or computer if unable or unwilling to do this at home (must be able to access their email and click on link to access questionnaires).

For those patients who do not have an email address or who are unwilling to use on-line questionnaires, we will offer the use of paper questionnaires filled out in the office or at home (via mail). Occasionally, patients may be asked to complete baseline questionnaires by paper after they consent to participate if their surgery is scheduled soon, as it may be more difficult for them to complete the on-line questionnaires before the surgery.

Office evaluation by the surgeon (or relevant staff) including anatomic outcome assessment will occur in the postoperative period

(typically 4 to 12 weeks after surgery) as well as additional scheduled postoperative visits consistent with the surgeons current practice pattern and non-scheduled problem-focused visits. Clinic visits post pessary placement may vary and it is anticipated that the majority of post-placement reporting will be direct from patients at the specified time points.

4.5.2.1 Baseline/Enrollment

Data collected at baseline prior to initiation of POP treatment in the PFDR-R and other PRDR are outlined in Table 5.

Table 5. Baseline Data Collection

Variable		PFDR-R Dataset	PFDR-IS Dataset
Patient Demographics/Characteristics			
Date of birth		X	X
Contact Information		X	
Race and ethnicity		X	X
Education level		X	X
Medical History			
Parity (vaginal and cesarean deliveries)		X	X
Menopausal status		X	X
Current estrogen treatment		X	X
Co-morbid conditions		X	X
Habits: Tobacco use		X	X
Prior POP therapy (pessary, conservative management)		X	X
Surgical History			
Hysterectomy		X	X
Prior POP surgery		X	X
Prior UI surgery		X	X
POP			
POP compartment(s)		X	X
POP signs and symptoms (e.g., urinary, bowel, sexual, other local)		X	X
Planned POP Treatment (surgical or nonsurgical)		X	

X = data collected

4.5.2.2 Operative Data

For patients receiving surgical management, participating surgeons will enter operative data into the PFDR-R following each surgical case. Operative data may vary slightly be level and includes information about the surgeries performed and intra-operative events, including:

- Date of surgery
- Use of antibiotic and venous thromboembolism (VTE) prophylaxis
- Type of anesthesia
- Surgical approach
- Surgical procedure(s) performed, including concomitant procedures
- Additional evaluations performed (digital rectal exams, cystoscopy)
- Intraoperative complications
- Operative time
- Estimated blood loss
- Discharge with Foley catheter
- Post-procedure antibiotics
- Date/time of hospital discharge

4.5.2.3 Pessary Placement Data

For patients receiving non-surgical management, the following data regarding pessary placement will be captured:

- Date of initial pessary fitting
- Type/size of pessary

4.5.2.4 Follow-up

After initiation of treatment, data collection will occur at approximately 2, 6, 12, 18, 24 and 36 months post-surgery/post-pessary placement. All data collection time points will allow wide windows in order to accommodate variations in clinical practice and patient management and maximize data collection.

Data to be collected at follow-up visits in the PDFR-R and other PFDR registries are listed in the table below.

Table 6. Follow-up Data Collection

Variable		PFDR-R	PFDR-IS
Patient Reported Outcomes			
Vaginal bulging		X	X
Re-operation for POP (surgical patients only)		X	X
Post-surgical pessary placement (surgical patients only)		X	O
Surgical intervention for POP (pessary patients only)		X	O
Permanent removal of pessary with reason for removal (pessary patients only)		X	O
Sexual activity/dyspareunia		X	X
Patient-reported AEs		X	O
PFDI-20		X	X
PFIQ-7		X	X
PISQ-12		X	X

PGI-I Prolapse		X	O
PGI- I Incontinence		X	O
ICIQ-SF		X	O
Pain		X	X
Generic QOL measure (SF-12)		X	O
Provider Reported Effectiveness and Safety Outcomes			
Anatomic evaluation by compartment		X	X
POP-Q		X	X
Post-treatment AEs		X	X
Surgical interventions and other re-treatment		X	X

X = data collected; O = optional, study-specific

5. Statistical Methods

5.1 Overview

Any analyses will be fully described in written and approved statistical analysis plans (SAP). Generally, descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Population characteristics (including demographics, medical history, procedures, comorbidities, and post-treatment variables) will be summarized into counts of non-missing data, mean, standard deviation, and minimum, maximum, median, 95% confidence interval of the mean for quantitative variables and counts and percentage with 95% confidence interval for categorical data. Surgical complications will be classified according to the Clavien-Dindo classification [Dindo 2004].

Effectiveness, quality of life and safety outcomes will be analyzed. Data from the Industry Sponsored Research Registry may, at the discretion of the AUGS Research Registry Committee, be incorporated into the aggregate data depending upon the data use agreements outlined between AUGS and Industry sponsor and the scientific question considered. Any reported analysis that includes data from the Industry Sponsored Research Registry will clearly indicate this. Analyses will be carried out based on subpopulations (including initial POP treatment versus re-treatment) where the number of patients is considered sufficient for analysis and interpretation. The characteristics of surgeries performed for POP will be reported. The distribution of patients and patient characteristics by treatment type and type of surgery will be described. Univariate and multivariable approaches will be used to identify factors associated with primary and secondary outcomes. The global association between use of surgical approach/technique and risk factors for complications or recurrence will be examined using time to logistic regression models or time to event analysis including Cox Proportional Hazards Models.

In order to minimize the influence of known and potential confounders of treatment outcomes, variables will be collected and utilized where appropriate during analysis for stratification and/or adjustment, including patient baseline characteristics (e.g., age, BMI, POP characteristics, medical history, concomitant medication use), treatment characteristics (e.g., primary vs. recurrent, compartment(s) repaired) and surgeon characteristics.

Any analyses specific to the Industry Sponsored Research Registry will be outlined and performed in accordance with the individual study protocols and statistical plans by the industry sponsor and, where

applicable, subject to reporting requirements of the FDA. At the conclusion of industry-sponsored 522 studies, the AUGS Research Registry Committee may perform secondary analyses of the Industry Sponsored Research Registry subject to the restrictions of the data use agreements outlined between AUGS and the industry sponsor.

5.2 Missing Data

Full details on handling of all missing data, which are common in observational studies, will be described separately in the SAP. In general, missing data will not be imputed and the data will be analyzed as they are recorded in the registry electronic case report forms (eCRFs).

5.3 Data Reporting

The main findings of the PFDR will be reported in a Registry Report at least annually and posted on the PFD Registry website. Status (e.g., enrollment statistics) and benchmarking reports will be provided periodically to participating sites and stakeholders. Following approach outlined in 5.1, Registry Reports will present aggregate efficacy and safety data for the following categories of surgical procedures: 1) Transvaginal Native Tissue; 2) Transvaginal Mesh Procedures – Permanent Synthetic; 3) Transvaginal Mesh Procedures - Biologic; 4) Sacrocolpopexy and 5) Obliterative Repairs and one non-surgical category: Pessary. Within each surgical category, data will be presented by anatomic prolapse compartment at enrollment: Anterior, Posterior, Apical (Table 2). Data from the Industry Sponsored Research Registry may be incorporated, at the discretion of the AUGS Registry Scientific and Steering Committees, into the aggregate data depending upon the data use agreements outlined between AUGS and Industry sponsor; any such addition will be clearly labeled.
Registry report Efficacy data included in the Registry Reports will include the Primary Effectiveness Endpoints (Section 4.4.3) and Secondary Efficacy and Quality of Life endpoints (Section 4.4.4) Only patients with a minimum of 12 months of follow-up after their index surgery will be included in Efficacy data in the Registry Report. Safety data will include the Primary Safety Endpoints outlined in 4.4.5 and Appendix A. Additional ancillary analyses may be reported on an ad hoc basis (See Section 6.7). At the participant's request, select measures may be reported to the Center for Medicare & Medicaid Services (CMS) to fulfill requirements for Physician Quality Reporting System (PQRS).

6. Registry Conduct

6.1 Governance

Registry Steering Committee – The work of the Registry will be guided by a Registry Steering Committee (RSC). This committee will be responsible for developing and implementing the strategic goals of the registry and is the governing body that oversees registry operations; including the successful implementation, monitoring and management of resources and activities. Please see Registry Steering Committee Charter available at http://pfdregistry.augs.org/governance.

Stakeholder Advisory Board – PFD Registry Stakeholder Advisory Board serves as the vehicle for key partners to support and provide input to the AUGS PFD Registry and to support and conduct clinical research and improve quality of care for women with PFD. See Stakeholder Advisory Board Charter available at http://pfdregistry.augs.org/governance.

Additional Committees – The Registry Steering Committee has the ability to designate committees or working groups to advance the work of the Registry and report back to the Steering Committee. Current Committees include, but are not limited to:

- *Research Registry Committee*. This Committee is responsible for overseeing the scientific content of the registry including data elements, design and implementation. The chair of the Scientific Committee is appointed by the AUGS Board of Directors for a three-year term. A broad group of urogynecologists, gynecologists, urologists and other relevant disciplines will be appointed to this committee by the Chair of Scientific Committee to ensure the Registry is responsive to the needs of physicians treating patients with PFD. This Committee also will review requests for data use and analysis. This Committee will develop additional sub-committees to assist in ensuring the scientific integrity of the Registry (e.g. Publications, Quality, Website) as needed.

Conflicts of Interest – Conflicts of interest (COI) shall be disclosed annually, via completion of the AUGS COI form, and then reviewed by the AUGS Governance Committee per AUGS policy. Members of the Research Registry Committee and the Chair and Vice Chair of the RSC must be free of relevant financial conflict of interest during their time of service on these committees. Other AUGS officers and members must comply with the AUGS conflict of interest policy (available at http://www.augs.org/p/cm/ld/fid=4).

6.2 Data Entry/Electronic Data Capture

All data will be collected and entered directly into the Quintiles | Outcome electronic data capture (EDC) system. Some patient-reported data may be collected on paper and entered into the registry by PFDR or site staff. Remote training for data entry procedures will be provided. All participating sites will have access to the data entered regarding the individual site's own enrolled patients. All sites will be fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering patient data into a secure internet-based EDC registry database via the eCRF. Providers and site personnel will be able to access their account with a username and password. A project-specific email address will be provided on the registry website portal page for use by anyone interested in participating in the registry or receiving more information about the registry. In addition, for registered users, Help Desk support is available for issues related to the registry and data collection. The Help Desk team is equipped to handle any operational or logistical questions.

All eCRFs should be completed by designated, trained personnel or a study coordinator, as appropriate. All changes or corrections to eCRFs will be documented in an automated audit trail and an adequate explanation is required.

6.3 File Retention and Archiving

The site agrees to keep relevant registry records, including the identity of all participating patients and all original signed informed consent forms (as applicable).

Studies conducted as part of the Industry Sponsored Research Registry participation may entail additional file retention specifications, which will be described in individual study protocols. In general, study records for Industry sponsored studies (e.g., original signed informed consent forms, source documents)

should be retained by the site according to local regulations, or as specified in the study contract, whichever is longer. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the study sponsor.

6.4 Quality Assurance

The database will be housed by Quintiles | Outcome in a physically and logically secure computer system maintained by Quintiles | Outcome in accordance with a written security policy. The system meets the standards of the International Committee on Harmonization (ICH) guideline E6R1 regarding electronic data handling and is available for audit upon request. The system also meets approved U.S. federal standards for the security of health information and is validated.

Due to the nature of the registry, it is anticipated that the majority of quality controls will be implemented through edit checks and data queries issued through the EDC system.

6.5 Data Management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries may be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis.

6.6 Protocol Amendments

Any changes in protocol will be reviewed and approved by the RSC. Changes to the protocol will be documented in written protocol amendments and the Stakeholder Advisory Board will be notified prior to implementation. No changes or amendments to this protocol may be made by the participating providers or other stakeholders unless such change(s) or amendment(s) has/have been fully discussed and approved by the RSC.

6.7 Requests for Ancillary Data Analyses

The RSC (described in Section 6.1) will develop written policies, for access and utilization of registry-generated data. Data analysis results may be requested for abstract submission to scientific meetings, development of manuscripts for peer-review journal submission, and scientific symposia. The Research Registry Committee also works with the RSC to ensure appropriate dissemination of treatment-related and clinical course related information to health authorities and stakeholders. These roles and policies will be codified in the committee charters.
The PFDR-R Registry will be used for research. Research will generally be

performed using PFDR-R data, because patients enrolled in the PFDR-R have provided informed consent for their participation. The Research Registry also has other advantages as a source of research data, including 1) more detailed data collection, 2) patient-reported quality of life and other outcomes, 3) nonsurgical (pessary) treatment outcomes and 4) likely more complete follow-up or longitudinal data.

Participating PFDR-R sites may publish or present the results of their own data and will be granted publication priority by the Publications Subcommittee for data solely originating from their site. Individual considerations for data access and use will not hinder the publication of full aggregate data analyses or registry results. The Research Registry Committee will meet at regular intervals to review incoming proposals for consolidated data analyses from any source, including financial sponsors of the registry, submitted via a common form comprised of information regarding the scientific basis for the proposal, the data required, the methods to be utilized in the analysis, the likely significance of the results and the proposed plan for publication or other dissemination of the registry results. The Research Registry Committee will provide recommendations to the RSC that include an assessment of the scientific validity of the proposal as well as its ranked priority for implementation.

6.8 Publication Policy

Any publication of the results from this registry must be consistent with the PFDR publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010.

Completed manuscripts involving data from more than one registry site must be provided to the Publications Sub-committee for review and comment, ideally, at least thirty (30) days prior to submission or presentation.

7. Safety Reporting

7.1 Definitions

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the registry. Intercurrent illnesses or injuries should be regarded as AEs.

Serious injury
Any injury or illness during the course of the registry that is any one of the following:

- life-threatening
- results in permanent impairment of a body function or permanent damage to body structure

- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

See Appendix for definitions of adverse events and other clinically important events.

7.2 Reporting to the FDA

User facilities are required to report suspected medical device related deaths to both the FDA and the manufacturers within 10 days of learning of its occurrence. User facilities are required to report medical device related serious injuries to the manufacturer only within 10 days of learning of its occurrence. If the medical device manufacturer is unknown, the serious injury is reported by the facility to FDA. Manufacturers have 30 days to report medical device related deaths and serious injuries to FDA, and 5 days to report events that require remedial action to prevent an unreasonable risk of substantial harm to the public health. All regulatory reporting for events reported in the PFDR-R remain the responsibility of the user facility.

8. Ethical and Regulatory Considerations

8.1 Guiding Principles

The study will be conducted in compliance with the US FDA Title 21 CFR Part 50 – Protection of Human Patients and/or Part 56 – Institutional Review Boards; the International Conference on Harmonization (ICH) GCP guidelines (May 9, 1997) as they apply to post-market, observational studies; the Declaration of Helsinki and its amendments; and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

8.2 Risks and Benefits of Patient Participation

Patient participation in the registry is considered of minimal risk. One potential risk is associated with the inadvertent release of personal medical data; however, every possible safeguard will be enacted during the conduct of this registry to prevent any breech of patient confidentiality from occurring (refer to Section 8.4).

One of the main purposes of the registry is to generate balanced evidence regarding treatments for PFD and improve patient outcomes. Patients that participate in the registry may not receive direct benefit, but the knowledge gained regarding comparative treatment outcomes could result in optimization of their future care as well as the care of other patients with PFD.

8.3 Patient Information and Informed Consent

An informed consent form (ICF) must be signed by the patient (or the patient's legally authorized representative) before her participation and enrollment in the Research Registry. All patients will complete a HIPAA authorization prior to enrollment. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to

participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file. A registry-specific ICF (and HIPAA Authorization for Release of Information) template will be provided to sites to facilitate the submission process.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study. Documentation of appropriate informed consent is subject to audit.

8.4 Patient Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon registry enrollment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any forms, reports, publications, or in any other disclosures, except where required by law. Patients will be informed about data handling procedures and asked for their consent at sites participating in the PFDR-R. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patient confidentiality will be strictly maintained.

8.5 Institutional Review Board

Consistent with local regulations and prior to enrollment of patients at a given site, the PFDR-R registry protocol will be submitted together with its associated documents (e.g., ICF) to the responsible central and/or local IRB for its review, as required. Patient enrollment will not start at any site before the registry has obtained written confirmation of a favorable opinion/approval from the relevant central or local IRB. The IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given that clearly identifies the registry, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IRBs during the course of the registry in accordance with local requirements. It is the responsibility of the site to have prospective approval of the registry protocol, protocol amendments, and informed consent forms, and other relevant documents, if applicable, from their local IRB and provide documentation of approval to the registry.

8.6 Separation of Industry-Sponsored Data

The credibility and integrity of the data and reports associated with the PFDR require that the Registry be free of commercial bias and influence. There is a common understanding that all governing policies are transparent and developed using an independent process, based on the best scientific evidence. One of the primary objectives of the PFDR is to provide a platform for industry sponsored studies required to fulfill the FDA's request for post-market surveillance for transvaginal mesh for POP and, in the future, potentially other surgical devices. In so much as industry sponsorship has the potential to create real or

perceived conflicts of interest with the PFDR as a whole or its other objectives, clear policies have been instituted to minimize this conflict and preserve the integrity, credibility and independence of the PFDR. The AUGS conflict of interest policy (available at http://www.augs.org/d/do/691) serves as the guiding document in this process (see also Section 6.1 Governance above). Data from industry-sponsored studies, including the 522 postmarketing surveillance studies, will be captured exclusively in the Industry Sponsored Research Registry. Industry-sponsored data will be kept distinct and separate from the Research Registry, with each individual industry-sponsored study collecting data in its own independent (and secure) "protocol" within the EDC. Participation in the Research Registry (PFDR-R) will be voluntary; sponsorship by a medical device company or other commercial interest is strictly prohibited. Only data submitted by surgeons or sites into the Research Registry will be used for an individual surgeon's or site's quality improvement activities or maintenance of certification, should the PFDR be approved for these purposes in the future. Data reporting and analyses from the Research Registry will be performed under strict guidance of the PFDR Scientific Committee independent of industry influence. All Registry Scientific Committee members must be free of relevant conflicts of interest. The RSC will be responsible for ensuring that transparent processes exist for access, use, analyses and publication of data from the PFDR. Corporate Sponsors will not be allowed to participate in the direct management of the PFDR and individuals who are employed by or engaged to represent a Sponsoring Company are not eligible to serve on the Registry Scientific Committee or serve as an expert advisor or reviewer on behalf of the Registry. As members of the PFDR Stakeholder Advisory Board, industry sponsors may request analyses of data from the Research Registry, subject to approval of the RSC and conducted by the Registry Scientific Committee.

9. References

Adams E et al. Mechanical devices for pelvic organ prolapse in women. Cochrane Database Syst Rev, 2004(2): CD004010.

Altman D et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011; 364(19): 1826-36.

Avery K et al. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004;23(4):322-30.

Barber MD, Walters MD and Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol 2005;193(1):103-13.

Barber MD et al. Defining success after surgery for pelvic organ prolapse. Obstet Gynecol 2009;114(3): 600-9.

Bump RC et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175(1):10-17.

Chmielewski L et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011; 205(1): 69 e1-8.

Clark AL et al. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2003; 189(5):1261-7.

Dindo D, Dimartines N and Clavien P. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.

Diwadkar GB et al. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009;113(2 Pt 1): 367-73.

Ellerkmann RM et al. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol 2001; 185(6):1332-7; discussion 1337-8.

FDA Safety Communication: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse. Urogynecologic Surgical Mesh: Update of the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse. July 2011. Available at: http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf. Accessed 21 June 2012.

Hu TW et al. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. Urology 2004; 63(3): p. 461-5.

International Committee of Medical Journal of Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications. October 2008. Available from http://www.icmje.org/urm_full.pdf. Accessed January 2011.

Jacobson GF et al. Hysterectomy rates for benign indications. Obstet Gynecol 2006;107(6): 1278-83.

Jelovsek JE, Maher C and Barber MD. Pelvic organ prolapse. Lancet 2007;369(9566): 1027-38.

Lamers BH, Broekman BM, and Milani AL. Pessary treatment for pelvic organ prolapse and health-related quality of life: a review. Int Urogynecol J 2011;22(6): 637-44.

Landefeld CS et al. National Institutes of Health State-of-the-Science conference statement: prevention of fecal and urinary incontinence in adults. Ann Intern Med 2008;148(6):449-58.

Luber KM, Boero S and Choe JY. The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol 2001; 184(7):1496-501; discussion 1501-3.

Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;4:CD004014. doi: 10.1002/14651858.CD004014.pub5.

Maher CM. Surgical management of pelvic organ prolapse in women: the updated summary version Cochrane review. Int Urogynecol J 2011;22(11): 1445-57.

Nygaard I et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA 2008;300(11):1311-6.

Olsen AL et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89(4):501-6.

Rogers RG et al. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int Urogynecol J Pelvic Floor Dysfunct 2003;14(3):164-8; discussion 168.

Srikrishna S, Robinson D, and Cardozo L. Validation of the Patient Global Impression of Improvement (PGI-I) for urogenital prolapse. Int Urogynecol J 2010;21(5):523-8.

Swift SE. The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol 2000; 183(2):277-85.

Whiteman MK et al. Inpatient hysterectomy surveillance in the United States, 2000-2004. Am J Obstet Gynecol, 2008;198(1):34 e1-7.

Wilson PD et al. Adult Conservative Management. 3rd International Consultation on Incontinence, ed. P. Abrams, et al.2005, Paris: Health Publication Ltd. 855-962.

Wu, JM, Matthews, CA, Conover, MM, Pate, V, and Funk, JM. Lifetime Risk of Stress Urinary Incontinence or Pelvic Organ Prolapse Surgery. Obstet Gynecol 2014; 123(6):1201-1206.

Yalcin I and Bump RC. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003;189(1):98-101.

Appendix : Adverse Event (AE) and Related Clinically Important Event Definitions*

	Event	Definition/Data Collected
Intraoperative complications	Bleeding requiring blood transfusion	yes/no, # of units of packed red blood cells
	Visceral organ injury (proctotomy, enterotomy, cystotomy)	Injury to the rectum, large intestine, small intestine, or bladder
	Vascular injury	Injury to a major blood vessel, diagnosed by imaging study or surgical intervention
	Ureteral kink/injury	Failure of one or both ureters to adequately deliver urine to the bladder, as determined either intra- or post-operatively. Management: a) Suture removed, ureteral kinking released without further intervention; b) Ureteral stent placed; c) Primary reanastomosis of transected ureter; d) Reimplanation; e) Percutaneous nephrostomy; f) Nephrectomy
	Urethrotomy	Unplanned piercing or creation of an opening in the urethra, recognized intraoperatively
	Aborted procedure due to intraoperative event*	Surgical procedure aborted due to an interaoprative event
	Mesh kit/device malfunction*	Any abnormal occurrence attributable specifically to the components of the mesh kit before or during placement, i.e. trocar releases from mesh material, abnormality of the protective sleeve surrounding the mesh material, etc. Recognized intraoperatively
Postoperative complications (occurring ≤12 weeks after index surgery only)	Ileus/bowel obstruction	Hypomotility, or partial or complete blockage of the GI tract associated with nausea or vomiting based on clinical or radiographic criteria
	Thrombotic events	Formation of a blood clot (thrombus) in an artery or vein requiring anticoagulation therapy. A thrombus can block blood flow at the point of clot formation or break free to block it elsewhere (embolism). Does not include prophylactic therapy
	Severe or acute cardiac events (e.g., myocardial infarction)	Any severe or acute cardiovascular condition including acute MI, unstable angina or cardiac mortality.
	Pulmonary Event	Pulmonary edema or pneumonia
	Cerebrovascular events	Cerebrovascular event
	Intensive care unit (ICU) admission*	Any unplanned admission to an intensive care unit
	Return to operating room (OR) to manage a complication during index hospitalization*	Return to operating room (OR) during the index hospitalization to manage a complication
Postoperative complications	Lower urinary tract infection	Urinary tract infection (UTI) based on clinical judgment or confirmation of a culture proven by lab criteria also includes empiric antibiotic treatment for symptoms thought to be secondary to UTI
	Infection of bone	Infection and noninfectious inflammation of

(occurring at any time point after surgery through 36 months)		the bone and surrounding muscles (e.g. pubic symphysis (osteitis pubis), sacrum (sacral osteomyelitis), or other bony structure)
	Vaginal infection	Infection of the vagina determined by a physician using clinical or radiologic indicators to be uncommon to vagina and requiring treatment
	Pelvic infection or abscess	Infection/cellulitis of the pelvic organs determined by physician using clinical or radiologic indicators and requiring treatment
	Other infection	Infection diagnosed using clinical or radiologic indicators not including vaginal infection, lower urinary tract infection, pelvic infection/abscess or infection/inflammation of bone
	Atypical vaginal discharge	New onset of vaginal discharge not suggestive of typical, common vaginitis
	Vaginal wall dehiscence	Separation of the vaginal tissue layers at the surgical site incision
	Vaginal scarring	De novo vaginal scar requiring medical or surgical intervention, or adversely affecting quality of life
	Vaginal shortening	A clinically significant decrease in total vaginal length requiring medical or surgical intervention, or adversely affecting patient quality of life
	Mesh exposure into vagina	The observation of mesh through the vaginal wall or epithelium. This condition is synonymous with mesh extrusion. Location (anterior, posterior, distal vagina/introitus, apex)
	Mesh erosion into viscera	Perforation of mesh into a hollow organ or viscus. Location (urethra, bladder, ureter, rectum, bowel - all that apply)
	Suture exposure in vagina	The observation of suture through the vaginal wall or epithelium. This condition is synonymous with suture extrusion. Location (anterior, posterior, distal vagina/introitus, apex)
	Suture erosion into viscera	Perforation of suture into a hollow organ or viscus. Location (urethra, bladder, ureter, rectum, bowel - all that apply)
	Neuromuscular disorder (including groin and leg pain)	A disorder or range of conditions associated with the dysfunction of nerves and/or muscles leading to pain, sensory loss, weakness or immobility. This would include groin and leg pain
	Pelvic pain (beyond 12 weeks post-surgery)	Any pain associated with worsening bother compared to preop occurring in the lower abdomen or genital area beyond 12 weeks post-operatively (excluding neuromuscular pain and dyspareunia)
	De novo vaginal bleeding (beyond 6 weeks	New onset or persistent vaginal bleeding

Postoperative complications (continued) [occurring at any time point after surgery through 36 months]	post-surgery)	beyond 6 weeks
	De novo or worsening dyspareunia	De novo: Any new onset pain associated with sexual activity that was not present during sexual activity preoperatively. Worsening: Any worsening pain associated with sexual activity compared to preoperative state. (Any incremental worsening compared to preop; does NOT include De Novo Dyspareunia)
	Fistula	An abnormal connection between two epithelium-lined organs that do not normally connect including vesicovaginal, rectovaginal, ureterovaginal, urethrovaginal, enterovaginal/colovaginal, enterovescial
	Sinus tract	A pathologic communication between a body cavity and an adjoining space (e.g. between vagina and peritoneal cavity through which fluid can drain)
	Hematoma	A localized swelling filled with blood resulting from a break in a blood vessel (abdominal, retroperitoneal, retropubic, obturator, vaginal, mons, other.)
	New or worsening voiding dysfunction	The new onset or worsening inability to completely empty the bladder during urination.
	New or worsening stress incontinence	The new onset or worsening involuntary loss of urine during period of increased abdominal pressure. Such events include laughing, sneezing, coughing or lifting heavy objects.
	New or worsening urge incontinence	The new onset or worsening involuntary loss of urine occurring for no apparent reason while suddenly feeling the need or urge to urinate.
	New or worsening constipation	New onset or worsening condition in which bowel movements occur less often than 3 times per week (NIDDK).
	New or worsening fecal incontinence	New onset or worsening uncontrolled loss of gas or stool (feces) through the anus.
	Hospital re-admission related to index surgery*	Any unplanned admission within 3 years of index surgery
	Re-operation to manage postoperative complications including mesh complication*	Any return to the operating room for complication, recurrent POP or new onset symptom such as SUI
	Death	

Events labeled with a (*) are clinically important events that are not strictly defined as AEs but are related and/or the secondary result of an adverse event that will be captured and reported by the registry.