# Prospective Randomized Controlled Trial Comparing Transvaginal Rectopexy and Ventral Mesh Rectopexy for Obstructed Defecation in Pelvic Organ Prolapse (PROD Trial)

National Clinical Trial (NCT) Identified Number: NCT05747027

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## Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Participants Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1. Protocol Summary

## 1.1 Synopsis

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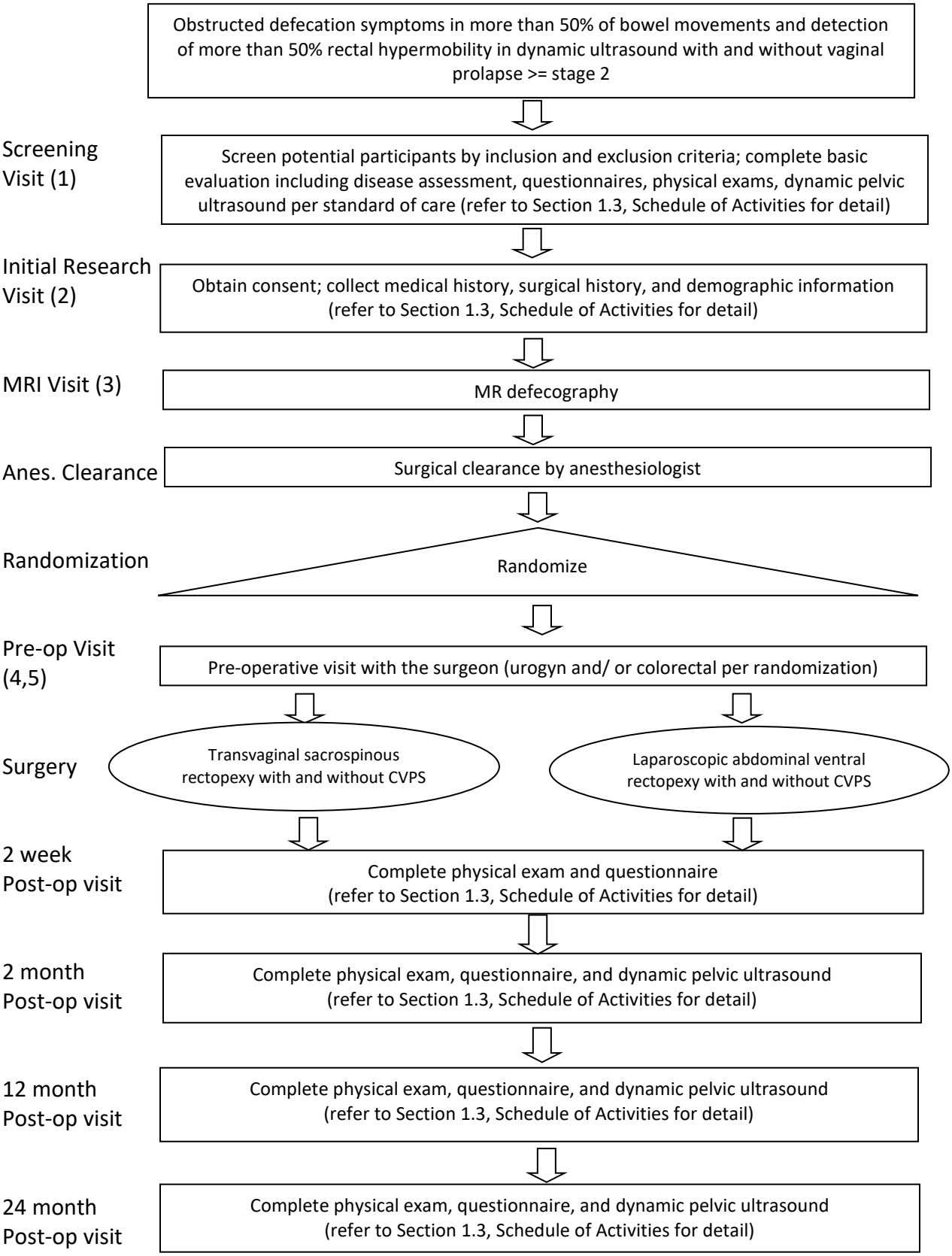
| **Title:** | Prospective Randomized Controlled Trial Comparing Transvaginal Rectopexy and Ventral Mesh Rectopexy for Obstructed Defecation in Pelvic Organ Prolapse (PROD Trial) |
| **Study Description:** | This is a collaborative 2-armed multi-center prospective clinical trial comparing: a) transvaginal sacrospinous rectopexy (TSR) with and without conventional vaginal prolapse surgery (CVPS); vs. b) laparoscopic abdominal ventral rectopexy (LAVR) with and without conventional vaginal prolapse surgery (CVPS). Women with vaginal prolapse who report obstructed defecation (OD) symptoms in more than 50% of their bowel movements with significant rectal hypermobility (more than 50% compression ratio in dynamic pelvic ultrasound) will be approached for enrollment. Eligible and consented participants will be randomized to undergo one of the two procedures: 1) laparoscopic abdominal ventral rectopexy with and without CVPS; 2) transvaginal sacrospinous rectopexy with and without CVPS. After the procedure, participants will be followed for 2-week, 2-month, 12-month, and 24-month post-operative visits. Symptom evaluation, pelvic exam, and dynamic pelvic ultrasound completed pre- and post-operatively will be used to compare the outcomes of the two procedures. |
| **Outcomes:** | **Primary Outcome:** Compare surgical success or failure in female participants with moderate to severe OD symptoms, and rectal hypermobility diagnosed by ultrasound, who are randomized to minimally invasive transvaginal sacrospinous rectopexy versus laparoscopic abdominal ventral rectopexy at 24 months after surgery. The primary outcomes will be measured by:<br>1. The degree of rectal hypermobility measured via dynamic pelvic ultrasound (i.e. compression ratio).<br>**Secondary Outcomes:**<br>a. Compare efficacy and safety of the surgery.<br>b. Compare the use of dynamic pelvic ultrasound imaging versus MR defecography to measure occult rectal hypermobility.<br>c. Develop and validate a computational finite element model and statistical shape modeling approach to describe the mechanics of normal defecation and the role of rectal and vaginal support deficiencies in causing OD symptoms. |
| **Study Population:** | 120 participants who are female, between the age of 18 and 80, and who may and may not have vaginal prolapse, who report OD symptoms in more than 50% of their bowel movements and with significant rectal hypermobility |
| **Phase:** | N/A |
| **Description of Sites/Facilities Enrolling Participants:** | Recruitment and informed consent will occur in two participating medical centers: 1) NorthShore University HealthSystem, and 2) Weill Cornell Medical Center- New York Presbyterian. |
| **Description of Study Intervention:** | **Laparoscopic abdominal ventral rectopexy:** This is an established surgical technique involving mesh implantation, commonly used to restore rectal support in women with obstructed defecation syndrome (ODS).<br>**Transvaginal sacrospinous rectopexy:** This is a novel minimally invasive surgery which directly suspends and stabilizes the rectal wall to pelvic ligaments with no external incision and no mesh implantation. This novel |

| | |
|---|---|
| | mesh-free operation may be a simpler, less invasive, and more anatomically accurate surgical approach for ODS. |
| **Study Duration:** | 60 months |
| **Participant Duration:** | 24 months |

## 1.2 Schema


Obstructed defecation symptoms in more than 50% of bowel movements and detection of more than 50% rectal hypermobility in dynamic ultrasound with and without vaginal prolapse >= stage 2
Screening Visit (1)
Screen potential participants by inclusion and exclusion criteria; complete basic evaluation including disease assessment, questionnaires, physical exams, dynamic pelvic ultrasound per standard of care (refer to Section 1.3, Schedule of Activities for detail)
Initial Research Visit (2)
Obtain consent; collect medical history, surgical history, and demographic information (refer to Section 1.3, Schedule of Activities for detail)
MRI Visit (3)
MR defecography
Anes. Clearance
Surgical clearance by anesthesiologist
Randomization
Randomize
Pre-op Visit (4,5)
Pre-operative visit with the surgeon (urogyn and/ or colorectal per randomization)
Surgery
Transvaginal sacrospinous rectopexy with and without CVPS
Laparoscopic abdominal ventral rectopexy with and without CVPS
2 week Post-op visit
Complete physical exam and questionnaire (refer to Section 1.3, Schedule of Activities for detail)
2 month Post-op visit
Complete physical exam, questionnaire, and dynamic pelvic ultrasound (refer to Section 1.3, Schedule of Activities for detail)
12 month Post-op visit
Complete physical exam, questionnaire, and dynamic pelvic ultrasound (refer to Section 1.3, Schedule of Activities for detail)
24 month Post-op visit
Complete physical exam, questionnaire, and dynamic pelvic ultrasound (refer to Section 1.3, Schedule of Activities for detail)

## 1.3 Schedule of Activities (SOA)

| **Procedures** | Screening Appt. | Initial Appt. +/- 30 days | MRI Appt. +/- 30 days | Anesthesia Clearance | Randomization | Pre-op | Day of Surgery | 2 wk Post-op +/- 5 days | 2 m Post-op +/- 10 days | 12 m Post-op +/- 10 days | 24 m Post-op +/- 30 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Demographics | | X | | | | | | | | | |
| Medical history | | X | | | | | | | | | |
| Surgical history | | X | | | | | | | | | |
| Randomization | | | | | X | | | | | | |
| Pre-op with surgeon | | | | | | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | |
| Research consent | | X | | | | | | | | | |
| Surgical consent | | | | | | | X | | | | |
| Surgical procedure | | | | | | | X | | | | |
| Surgeon's Report | | | | | | | X | | | | |
| Physical exam | X | | | | | | | X | X | X | X |
| Dynamic pelvic ultrasound | X | | | | | | | | X | X | X |
| MR defecography | | | X | | | | | | | | |
| Anesthesia Clearance | | | | X | | | | | | | |
| Bowel habit | X | | | | | | | X | X | X | X |
| POPQ assessment | X | | | | | | | | X | X | X |
| PFDI assessment | X | | | | | | | | X | X | X |
| Pain scale | X | | | | | | | X | X | X | X |
| Pain medication use | X | | | | | | | X | X | X | X |
| Activity scale | X | | | | | | | X | X | X | X |
| Impression of improvement | | | | | | | | | X | X | X |
| PFIQ | | | | | | | | | X | X | X |
| SF-36 | | | | | | | | X | X | X | X |
| EQ-5D | | | | | | | | | X | X | X |
| Brink scale | | | | | | | | | X | X | X |
| Research Participation | | | | | | | | | | | X |
| Adverse event/ unanticipated problems | | | X | X | X | X | X | X | X | X | X |

# 2. Introduction

## 2.1 Study Rationale

Obstructed defecation (OD), defined as incomplete emptying of stool, is a widely prevalent disorder in women's health, occurring in roughly 25% of constipated women and resulting in major quality of life (QOL) and healthcare burdens (1-4). Symptoms include incomplete defecation, rectal pressure from retained or "pocketed" stool, and need for manual assistance to complete bowel movements. OD is often chronic, impacting some women for their entire adult lives. Successful management has been impaired, historically, by deficiencies relating to both diagnosis and treatment (5-7). First, there has been a persistent misconception that OD in the absence of dyssynergia (i.e., uncoordinated contraction of pelvic floor) results from prolapse of the posterior vaginal wall ('rectocele') and improves after its repair (5, 7). In fact, prior studies have confirmed that this form of OD results from support defects involving the rectum rather than vagina (8-10), and moreover that rectocele repairs are unreliable in relieving OD symptoms (6, 7). Recent work from our center confirmed rectal detachment and hypermobility to be the major determinants of OD in the absence of dyssynergia irrespective of the presence of a rectocele (8). Secondly, traditional diagnostic modalities to assess rectal support as the source of OD are expensive (e.g. MR defecography) and/or invasive (e.g. anal manometry), and often generate findings with unclear clinical correlation and impact on care (11). Finally, available surgeries to repair rectal support defects have been limited to invasive transabdominal or perineal methods (15,16,17), typically involving mesh implantation and reserved for severe cases, e.g. those with overt rectal prolapse. Laparoscopic or open ventral mesh rectopexy is the most widely accepted operation to stabilize rectal support (12, 13).

Our urogynecology division's dedicated Women's Bowel Clinic has focused substantial research effort on OD in women, and recent publications lay the foundation for the present study. On the diagnostic front, we established and validated a novel, anatomically-based and statistically robust criteria for diagnosing OD using dynamic pelvic ultrasound. We affirmed that OD symptoms in the absence of dyssynergia were associated with rectal support defects (4, 9, 10) and, contrary to conventional wisdom, had no relationship to vaginal prolapse / rectocele defects. During sonographic evaluation the presence or absence of rectal hypermobility, quantified using a new "compression ratio" metric developed and validated as part of this work, was highly predictive of the presence or absence of OD and appeared to obviate the need for MR defecography (5, 8, 14). On the surgical front, we developed a minimally invasive transvaginal surgery to directly suspend and stabilize the rectal wall to pelvic ligaments with no external incision, no mesh implantation, and thus far no significant morbidity (15). Our published case series demonstrated successful attachment of the rectal support defect, alleviation of OD symptoms and improved QOL in nearly all participants. This novel mesh-free operation appeared to be markedly simpler, less invasive, and more anatomically correct in contrast to standard laparoscopic abdominal ventral rectopexy.

Based on this exciting preliminary data, the overall goal of this proposal is to explore the potential for an improved treatment outcome for women suffering OD symptoms, utilizing newly developed diagnostic procedures based on dynamic pelvic ultrasound, a new surgical approach (transvaginal sacrospinous rectopexy), and an improved understanding of the physics of defecation. We believe a prospective, randomized comparison of the novel (transvaginal sacrospinous rectopexy) to traditional (laparoscopic abdominal ventral rectopexy) surgical methods across two institutions is an essential next step. We are testing the hypothesis that OD symptoms in the absence of dyssynergia primarily result from deficiencies in rectal support and that patients presenting with OD symptoms with and without vaginal prolapse undergoing our new diagnostic evaluation and surgical treatment will have improved outcomes relative to the current standard of care at 24 months after surgery. Our study is designed to evaluate primary and secondary outcomes relating to the two rectopexy procedures on OD at 24 months follow up across two institutions. This clinical data will be complemented by a computational modeling approach that aims to provide insight into the most likely contributors to OD symptoms, i.e. vaginal versus rectal support defects.

## 2.2 Background

1. **Constipation and obstructed defecation (OD) symptoms impact a large female population.**
   Accounting for more than 2 million clinic visits per year, constipation is one of the most common problems seen by primary care physicians, colorectal and urogynecology surgeons. (10, 16). In broad terms, constipation can be

classified as either normal-transit constipation (often coexisting with irritable bowel syndrome), OD, or slow-transit constipation. Each of these conditions may occur in isolation or may coexist, and it is often difficult to predict which patients have isolated or concomitant pathologies. Isolated defecatory dysfunction is thought to be present in 25% of patients with chronic constipation (1, 3, 17). OD is a common condition that affects approximately 7% of all adults, but 15-20% of adult women (4, 18-20). Although the etiology of OD symptoms continues to be debated, it is hypothesized that the higher prevalence observed in women could be due to damage incurred by pelvic floor soft tissues and nerves during vaginal delivery (21, 22).

2. **The anatomic and pathophysiologic changes associated with OD are varying and incompletely understood, and traditional surgical methods have often been based on incorrect assumptions.**
   OD may occur alongside other anatomical abnormalities such as pelvic organ prolapse (POP), internal rectal prolapse and/or solitary rectal ulcer, and/or functional factors relating to neuromuscular control. In trying to identify OD cases that are due to anatomic causes and therefore may be addressed with surgical repair (11), gynecologic surgeons have often assumed a causative relationship between OD symptoms and POP with a particular focus on rectoceles (posterior vaginal POP). However, available evidence indicates that this assumption is incorrect, as the severity of POP in participants with OD is not significantly different from that found in asymptomatic controls (23); in fact, at most, only weak associations have been identified between OD symptomatology and stage of rectocele. Similarly, the surgical repair of POP, and specifically the repair of rectoceles, has been associated with only limited improvements in OD symptoms regardless of the surgical approach (1, 2, 24-26). These findings suggest that key aspects underlying OD in the female population have been overlooked, misunderstood, or have yet to be quantified sufficiently, and that the conventional wisdom among gynecologic surgeons focusing on POP as a primary cause of OD appears to be unfounded.
   There is substantial evidence to suggest that OD symptoms may, in fact, be predominantly caused by a disorder in anorectal structure and/or function; that is, a problem resulting from deficient rectal rather than uterovaginal support (23). Unfortunately, several factors have limited our ability to reliably recognize and treat rectal support defects in women with OD. On the diagnostic level, defecography has remained a limited modality due to expense, patient inconvenience, and poor correlation between abnormal defecography findings and severity of OD symptoms. On the treatment front, existing rectal support surgeries have been relatively invasive and thus reserved for severe cases, and to-date there has been no minimally invasive surgical repair. These are critical knowledge and technology gaps relating to our understanding of key structural defects, resulting in inadequate solutions (diagnostic and surgical) for women suffering from this condition.

3. **No single test has been proven definitive or optimal for the evaluation of OD.**
   A thorough medical history should be obtained in all patients with OD, as the condition may be multifactorial and numerous factors relating to diet, medications and neuromuscular function may be directly or indirectly linked to symptoms (2). Physical exams are essential as an initial workup and should include inspection of the anorectal region and rectum to detect external signs of anal disease, POP and/or descending perineum syndrome. Imaging modalities have proven to be useful in identifying structural defects associated with OD symptoms (27). OD symptoms are of the most common symptoms leading to dynamic evaluation of the pelvic floor via imaging (28). Magnetic resonance (MR) imaging defecography was introduced in 1993 (29) and is increasingly used to evaluate pelvic floor dysfunction, particularly in complex cases involving defecatory symptoms. Dynamic MR defecography enables real-time evaluation of pelvic floor dysfunction including descending perineum syndrome, rectal prolapse, rectal intussusception, an enterocele or rectocele (30-35). The American College of Radiology has stated that both the fluoroscopic defecography and MR defecography with rectal contrast are appropriate and equivalent with respect to the evaluation of pelvic floor disorders involving all compartments of pelvic support; however, MR defecography is preferred for the assessment of defecatory dysfunction (36).
   Nevertheless, no single test has been established as definitive for the evaluation of pelvic floor and/or defecatory dysfunction, and the expense and inconvenience associated with MR defecography make it difficult to utilize on a wide scale. Most tests, including clinical examination, rely on patient collaboration and often induce embarrassment with some degree of psychological inhibition. The unnatural clinical environment during testing may provoke 'laboratory' artifact. Thus, interobserver reproducibility for many anorectal tests tends to be poor and abnormal test

results correlate poorly with symptoms (11). Lack of a reproducible, patient-friendly, highly accessible and cost-effective diagnostic test for rectal support defects is a significant unmet need.

4. **The role of rectal support in normal defecation is unknown.**
   The processes of normal rectal continence and evacuation are regulated through the coordinated interaction of multiple neuromuscular pathways and guided by mechanical support provided to the rectum (37-39). While these processes are complex, the functional endpoint that must be achieved is simple -- the body must generate intrarectal pressures that exceed atmospheric pressures externally, and the direction of that pressure gradient should pass through a relaxed anal sphincter. Failure to accomplish this results in symptoms of OD. Within the pelvis, the visceral organs are normally restrained from undergoing large motions, allowing for the passage of feces. However, when key structural defects exist, the motions of pelvic organs may no longer be optimally restrained, resulting in outlet obstruction or redirection of feces away from the anal canal. It has been previously suggested that for complete rectal prolapse to occur some, if not all, of the major supporting mechanisms of the rectum must be at least partially compromised (40, 41). While the rectum measures 12 to 15 cm in length, it is the lower half to one third that bears supportive attachments to other structures. Apically, the rectum is limited by the anterior peritoneal reflection that occurs at 7-9 cm from the anal verge in men and at 5-7.5 cm from the anal verge in women (42-44). Lateral support is provided by the lateral ligaments or stalks of the rectum; while anterior and posterior support are provided by the visceral pelvic fascia of Denonvilliers and the rectosacral fascia (a.k.a the fascia of Waldeyer), respectively (42, 43, 45). The superior/posterior aspect, which closely follows the sacral hollow, is entirely extra-peritoneal. The specific role of these supports in allowing for normal defecation are currently unknown and this limits our understanding of why OD occurs and how best to repair it.

## 2.3 Risk/Benefit Assessment

### *2.3.1 Known Potential Risks*

**Pelvic Exam**

There is no immediate or long-range risk from a speculum exam and a quantified assessment of prolapse. The exam may create mild transient discomfort.

**Written Questionnaires & Verbal Interviews**

Answering these questions may make some participants temporarily uncomfortable. While not specifically addressed in the instructions, participants may elect not to answer some personal questions. All acquired information will be kept confidential by identifying the forms with study numbers only, keeping the results and the list linking names to study numbers in a password-protected database. Access to file cabinets containing paper copies will only be granted to the PI and study coordinators.

**Dynamic Pelvic Ultrasound**

Ultrasounds are minimally invasive, part of routine urogynecology care, and conducted by trained medical personnel. The exam may cause transient, mild discomfort, but pose little to no immediate or long-range risk.

**MR Defecography**

The defecography may cause discomfort due to imaging in a closed environment, participants can stop the imaging anytime during the test if they feel uncomfortable. Patients at risk for injury from MR scans are those with pacemakers, aneurysm clips, or shrapnel fragments. There is a minimal risk of skin burns from the radiofrequency (RF) coil. The defecography poses little to no long-range risk.

**Surgical Procedures**

For the surgical procedure, standard risks of surgery apply including bleeding, infection, and injury to nearby organs including the bowel, bladder, and ureters. There is a potential risk of pain following the surgical procedure. There is potential mesh related risks including mesh erosion, pain, infection, and fistulas.

### *2.3.2 Known Potential Benefits*

Participants may receive direct personal benefits from participating in this research study. An immediate potential benefit of the study is a thorough assessment of obstructed defecation symptoms. All participants will complete a basic evaluation in which they will complete a disease assessment, questionnaires related to symptoms, physical exams, and dynamic pelvic ultrasound. Participants will have the opportunity to review this information with the participant's provider. Participants who are randomized to undergo rectopexy may benefit in the long-term with obstructive defecation symptom improvement.

### *2.3.3. Assessment of Potential Risks and Benefits*

We believe that the risks and benefits to the participants are balanced in this study design. Exam, questionnaires, and imaging used in the study are minimally invasive and part of routine urogynecology care. While standard risks of surgery apply to the surgical procedures, previous studies have demonstrated the safety of the two procedures. If participants in either treatment group develop new symptoms after surgery, treatment is available. Currently, patients with ODS receive treatment without follow-up that would allow sufficient assessment of the safety and efficacy of the surgical outcome, which could otherwise guide more effective clinical decisions.

## 3. Outcomes and Measurements

**Primary Outcome:** Compare surgical success or failure in female participants with moderate to severe OD symptoms, and rectal hypermobility diagnosed by ultrasound, who are randomized to minimally invasive transvaginal sacrospinous rectopexy versus laparoscopic abdominal ventral rectopexy at 24 months after surgery. The primary outcomes will be measured by:

1. The degree of rectal hypermobility measured via ultrasound (i.e. compression ratio).
    *a.* "Compression ratio" will be calculated as a means to quantify the relative change in length of the rectovaginal septum (RVS), in other words the degree of hypermobility / sliding rectum, and is expressed as a percentage using the following formula: $CR$ = (RVSr – RVSv)/ RVSRr * 100, where RVSr (Rectovaginal Septum) and RVSv represent the RVS length at rest and Valsalva.

The criteria for surgical failure will be defined as follows:

1. A participant will be considered a <u>surgical failure</u> if:
    a. Rectal hypermobility with compression ratio more than 20% is detected via ultrasound.
2. Otherwise, a participant will be considered a <u>surgical "success"</u>.

**Secondary Outcome:**

- Compare efficacy and safety of the surgery measured by:
    1. Postoperative pain - Participants will complete the Pain Scale (67) and an assessment of pain medication use preoperatively, and then at 2 weeks and 2, 12, and 24 months postoperatively.
    2. Postoperative functional activity level – Participants will complete the Activity Assessment Scale (68) which measures functional activity preoperatively and then at 2 weeks and 2, 12, and 24 months postoperatively.
    3. Global improvement in bladder function – Participants will complete the Patient Global Impression of Improvement (69) at 2, 12 and 24 months postoperatively.
    4. Pelvic Floor Distress Inventory (PFDI) – Prolapse and colorectal symptoms as assessed by the Pelvic Organ Prolapse Distress Inventory (POPDI) and Colorectal Anal Distress Inventory (CRADI) (short-term) and urinary and colorectal symptoms as assessed by the Urinary Distress Inventory (UDI) and CRADI (long-term) subscales at 2, 12, and 24 months postoperatively.
    5. Quality of life measured by Pelvic Floor Impact Questionnaire (PFIQ) (65), Short Form Health Survey (SF-36) (70), EuroQol-5D (EQ-5D) (71) at 2, 12 and 24 months postoperatively. The SF-36 will also be administered to a subset of participants 2 weeks post-operatively to allow validation of the Pain and Activity Assessment Scale.

6. Pelvic muscle strength measured by the Brink Scale at 2, 12, and 24 months postoperatively (72).

- Compare the use of posterior compartment dynamic pelvic ultrasound imaging versus MR defecography to measure occult rectal hypermobility.
- Develop and validate a computational finite element model and statistical shape modeling approach to describe the mechanics of normal defecation and the role of rectal and vaginal support deficiencies in causing OD symptoms.

# 4. Study Design

## 4.1 Overall Design

This is a collaborative multi-center 2-arm clinical trial comparing: a) transvaginal sacrospinous rectopexy (TSR) with and without conventional vaginal prolapse surgery (CVPS); vs. b) laparoscopic abdominal ventral rectopexy (LAVR ) with and without conventional vaginal prolapse surgery (CVPS) for ODS. A standardized common protocol for enrollment, treatment and data collection will be employed by the Clinical Sites and coordinated by the Data Coordinating Center (DCC). Women with and without vaginal prolapse who report OD symptoms in more than 50% of their bowel movements with significant rectal hypermobility (more than 50% compression ratio in dynamic posterior compartment ultrasound) will be approached for eligibility, consent, and enrollment. Participants who meet eligibility criteria and have provided informed consent will be randomly assigned to either abdominal or transvaginal rectopexy procedure (12, 62-64). Prior to randomization, eligible participants will undergo chart review by the anesthesiologist to ensure medical eligibility for both procedures.

Participants will receive the allocated transvaginal sacrospinous rectopexy surgery along with or without CVPS or laparoscopic abdominal ventral rectopexy surgery with or without CVPS as indicated for each individual and as determined before surgery (exceptions are allowed during the surgery if the surgeon decides that changing the surgical plan is in the best interest of the patient; this will be recorded as a protocol deviation). CVPS includes vaginal prolapse repair surgeries (anterior vaginal repair, posterior repair, and vault suspension) and abdominal prolapse repair surgery (sacrocolpopexy). If the participants report stress urinary incontinence at baseline, they will also receive a Tension-Free Vaginal Tape (Advantage FitTM, Boston Scientific). The primary objective of the surgical intervention is to compare the surgical success of rectal hypermobility surgery using TSR to surgery using LAVR 24 months postoperatively. The secondary objectives include comparing the change in pelvic floor disorder symptoms including OD and fecal incontinence symptoms, QOL and the incidence of perioperative and postoperative complications of these two rectal suspension procedures. We will also describe the motivations and barriers for individual women's participation in women's health research at 24 months after surgery in all participants. Data collection will occur at baseline, surgery and during hospitalization, and at 2 weeks, and 2-,12-, and 24-months postoperatively.

## 4.2 Scientific Rationale for Study Design

**Ultrasound indicators of rectal support defects in women with obstructive defecatory symptoms (48)**
This retrospective cohort study included 65 women who were referred to our urogynecology clinic because of varied pelvic floor disorders between January 2013 and January 2014. Patients completed a standardized interview including PFDI-20 questionnaire and received a standard examination, and assessment of their pelvic floor by 3D EVUS. Women were categorized to case (with OD symptoms) and control (without OD symptoms) based on their answers to Questions 7, 8 and 14 on the PFDI-20 (CRADI) questionnaire. In ultrasound images, women with OD symptoms had a significantly shorter span of attachment between the rectum and posterior vaginal

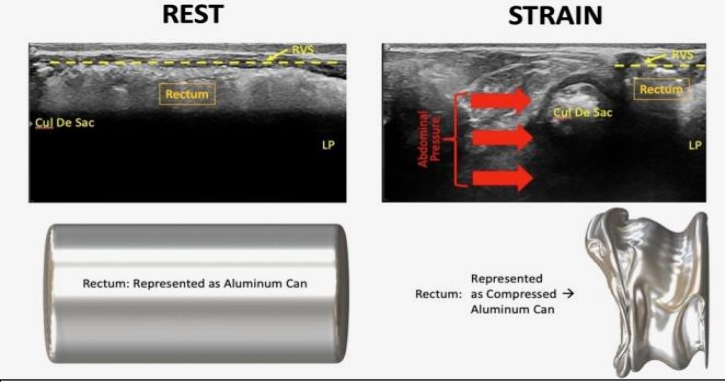



**Figure 1:** 2D dynamic endovaginal posterior compartment ultrasound of a patient with obstructed defecation symptoms at rest (left image) and at strain (right image). Rendering of an aluminum can is used to illustrate the concept of the rectal compression seen above. LP: Levator Plate, RVS: Rectovaginal Septum

wall (i.e. deeper cul de sac), and also had significantly increased descent of the cul de sac toward the anorectal junction when intraabdominal pressure was increased (Figure 1). A hypermobile 'sliding rectum' was observed that appeared to alter the fundamental biomechanics of defecation. These rectal mobility findings were extremely consistent among women reporting OD symptoms and not seen among asymptomatic controls.

**Compression Ratio Measured Via Dynamic Ultrasound and Validated Against MR Defecography is a Strong, Independent Predictor of OD**

As part of the above study, we established and validated a novel dynamics ultrasound measure ("compression ratio") to quantify this observed rectal sliding / hypermobility. The term "compression" was initially utilized because the rectum, during dynamic ultrasound, appeared to behave like an empty aluminum beverage can being compressed from its ends (Figure 1, bottom). As the cul de sac descended toward the anorectal junction with increased intraabdominal pressure, the rigid support of the probe anteriorly (i.e. bottom of ultrasound image) caused the descent of the cul de sac to be linear, making it appear as if it was sliding and folding on itself relative to the posterior vaginal wall. In participants without OD symptoms, little to no sliding was observed. The compression ratio (see approach for details) in our study proved to represent a strong and independent predictor of both the presence or absence of OD symptoms and the severity. The risk of OD symptoms was 32 times greater among those with a high compression ratio (≥14) compared to those with low compression ratio (<14), after controlling for age, BMI, parity, stool type, and BM frequency per week. A similar compression ratio was also calculated using measurements obtained by MR defecography. While MR measurements added meaningfully to our conclusions, the absence of a probe anteriorly resulted in a less vivid "crushed can" appearance when compared to dynamic ultrasonography. Thus, the less expensive and more patient- friendly in-office dynamic ultrasound appeared to be superior to MRI with regard to OD evaluation.

**OD Symptoms lack a correlation to rectocele**

It is worth emphasizing that along with the strong and robust correlations observed between OD symptoms and US-detected rectal hypermobility, our findings indicated a clear lack of correlation between OD symptoms and the presence or absence of rectocele as diagnosed via pelvic examination. While posterior vaginal compartment prolapses (i.e. rectoceles) may certainly account for bothersome symptoms including vaginal bulging and laxity, rectoceles appear to have essentially no relationship to obstructive defecation which was related to only one anatomic finding: excessive mobility of the rectum that is usually occult and easily detected by ultrasound. This core observation would, arguably, make it unsurprising that rectocele repairs have performed poorly to resolve obstructive defecation symptoms (24, 25). Furthermore, this diagnostic/anatomic finding provided the basis for our proposed surgical approach, transvaginal sacrospinous rectopexy.

**OD symptoms persist after conventional vaginal prolapse repairs at 2 years follow up (5)**

The previous finding regarding the role of POP was further demonstrated when we performed a sub-analysis of two major clinical trials performed by the Pelvic Floor Disorders Network: the Colpopexy and Urinary Reduction Efforts (CARE) trial and the Operations and Pelvic Muscle Training in the Management of Apical Support Loss (OPTIMAL) trial (55, 56). The study aimed to address 2 questions: 1) is any conventional vaginal prolapse repair effective in curing OD symptoms, and 2) is there evidence to suggest that a sacrocolpopexy will increase the risk of worsening or newly onset OD symptoms?

Regardless of trial, OD symptoms were present in more than half of the patients at the initial visit before the surgical intervention and interestingly about one third of the patients were symptomatic at the 24 -month follow- up interval in all conventional vaginal prolapse surgeries, with or without posterior vaginal wall repair (353 participants from OPTIMAL and 279 participants from CARE). It is also important to note that about 1/4 of the patients experienced worsening of their OD symptoms in the absence of anatomical failure. These data further support our overall hypothesis for this proposal that OD symptoms primarily result from structural defects in rectal support and not as a result of a loss in vaginal support, challenging the current standard for surgical treatment.

**Statistical shape modeling during evacuation suggests pelvic floor defects contribute to OD (57)**

This study used MR defecography and statistical shape modeling to identify variation in pelvic floor shape. 16 women underwent MR defecography and were sorted by Group: case with OD symptoms (N=9) vs control (N=7) (57). The pelvic floors were segmented at the mid-sagittal slice as spline curves and a statistical shape analysis was performed. These results support the hypothesis that the mid-sagittal shape of the pelvic floor deforms significantly during evacuation and differs significantly between women with and without OD symptoms. Women with OD symptoms had a hyper-relaxed pelvic floor—with lower, straighter levator plates and straighter level III support (Figure 2). Interestingly, levator plate relaxation and perineal body straightening were similar during evacuation, indicating that the differences between groups observed in this study were structural rather than functional defects.

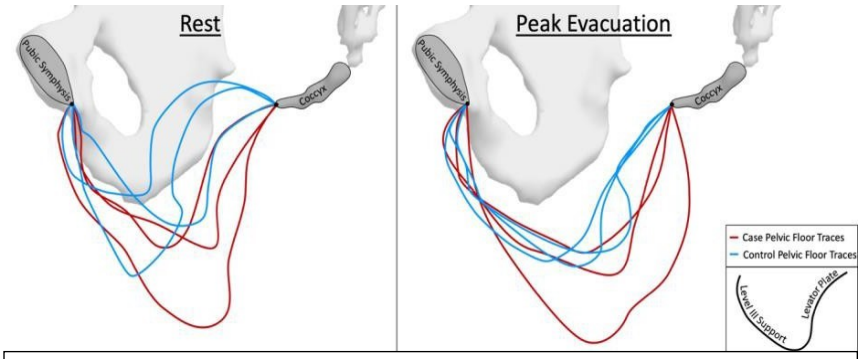



**Figure 2:** Illustrations of midsagittal pelvic floor traces (the midsagittal slice of the pelvic floor muscles, including the levator ani and level III vaginal support structures, that run from the pubic symphysis to the tip of the coccyx) from 3 asymptomatic control women (blue) and 3 women with obstructed defecation symptoms (red) at rest and during peak evacuation. These midsagittal traces were segmented from MR defecography images. On average, the control levator plates appeared better supported (as demonstrated by more dramatic curvature and elevation) than levator plates at both rest and peak evacuation in ODS participants[17]. This supports that levator plate relaxation (as demonstrated by a straighter and more vertical levator plate) is likely either a contributing mechanism or the result of obstructed defecation symptoms.

**Transvaginal sacrospinous rectopexy is safe and feasible for treating OD (15)**

This was a prospective case series study performed during December 2018-July 2020 and aimed to investigate the safety, efficiency, and durability of transvaginal sacrospinous rectopexy in women with OD symptoms and significant rectal hypermobility/folding (15). 20 patients underwent the procedure and completed the follow up at 2 and 12 months postoperatively. Statistically significant improvements were observed in all OD symptoms and subjective improvement (94.7% ± 13.4 and 90.6% ± 18) at 2 and 12 months after the surgery, respectively. Mean rectal compression ratio, detected via ultrasound, improved from 45.5% ± 18.4 preoperatively to 9.2% ± 13.7 at 2 months ($p < 0.0001$) and 19.6% ± 14.4 at 12 months ($p<0.0012$). Surgical failure, defined as combined subjective (OD symptoms > 50% of bowel movements) and anatomical failure (rectal compression ratio >25%), occurred in two patients. Overall, this study demonstrated that transvaginal sacrospinous rectopexy was safe, feasible, and effectively treated OD symptoms within this cohort of women undergoing POP surgery with rectal hypermobility confirmed by dynamic ultrasound.

**The proposed Latin hypercube parametric study based on finite element analysis and statistical shape modeling was successful in identifying the relative contributions of urethral support (53, 54)**

In a recent set of publications (53, 54), we utilized the finite element method and statistical shape modeling to elucidate the role of supportive tissues on the urethra during Valsalva. While these papers focused on the urethra, the methods and workflow will be similar to that utilized by this proposal. A finite element model of the urethra and its supports was created (Figure 3). Material properties were varied using Latin hypercube sampling to perform a sensitivity analysis resulting in 50 simulation outcomes where the motion and shape of the urethra was predicted and compared to those obtained from clinical measurements from 76 total patients ranging from no, mild, to severe SUI (excluding women with a low urethral closure pressure, i.e. focusing on patients whose level of continence was likely resulting from the integrity of their structural support). The results showed that a reduction of the urethral stiffness and/or the parameters governing the stiffness of the perineal membrane resulted in simulated urethral motions and shapes associated with stress urinary incontinence. This represents a novel use of finite element modeling and statistical shape modeling to provide a mechanical basis explaining underlying clinical observations.

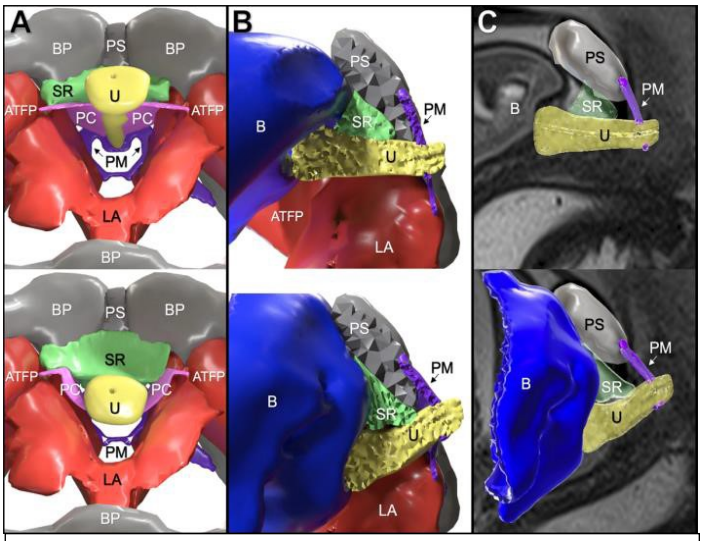



**Figure 3:** Screenshots of the baseline finite element model at rest (top) and peak Valsalva (bottom). A) Images from the perspective of the sacrum facing anteriorly and inferiorly. B) Images from the patient's right side with a midsagittal cut so the urethra can be seen clearly. C) Displays the same model view as B, but with the patient's dynamic MRI images overlayed to demonstrate the agreement between the final model and in vivo imaging.

### 4.3 Justification for Dose

Not Applicable.

### 4.4 End of Study Definition

A participant is considered to have completed the study if she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA), Section 1.3.

## 5. Study Population

### 5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Female, between the age of 18 and 80
2. OD symptoms as indicated by an affirmative response to either questions 7, 8 or 14 of the Pelvic Floor Distress Inventory (PFDI):
    a. Do you feel you need to strain too hard to have a bowel movement?
    b. Do you feel you have not completely emptied your bowels at the end of a bowel movement?
    c. Does part of your bowel ever pass through the rectum and bulge outside during or after a bowel movement?
3. Rectal hypermobility defined as a compression ratio greater than 50% according to ultrasound
4. Patient planning on undergoing surgery for the repair of pelvic organ prolapse within the next 12 months
5. Patient who is not pregnant and does not intend to become pregnant in the next 2 years
6. Available for 24-months of follow-up
7. Stated willingness to comply with all study procedures and availability for the duration of the study
8. Able to complete study assessments, per clinician judgment
9. Able and willing to provide independent written informed consent

10. Stable cardiovascular and respiratory status to meet candidacy in vaginal or laparoscopic surgeries

## 5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Contraindication to abdominal (history of severe intrabdominal surgery) and transvaginal rectopexy in the opinion of the treating surgeon
2. History of previous surgery that included any type of surgery for rectal prolapse
3. Pelvic pain or dyspareunia due to levator ani spasm that would preclude a PMT program
4. Previous adverse reaction to synthetic mesh
5. Current cytotoxic chemotherapy or current or history of pelvic radiation therapy within 12 months
6. History of two inpatient hospitalizations for medical comorbidities in the previous 12 months

## 5.3 Lifestyle Considerations

Not Applicable.

## 5.4 Screen Failure

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened.

## 5.5 Strategies for Recruitment and Retention

Recruitment and informed consent will occur in two participating medical centers: 1) NorthShore University HealthSystem, and 2) Weill Cornell Medical Center- New York Presbyterian. Participants will be recruited from principal investigator and colleague's patient population. Female, between the age of 18 and 80, with and without vaginal prolapse who report obstructed defecation symptoms in more than 50% of their bowel movements with significant rectal hypermobility will be contacted directly during outpatient clinic visit to learn more about the study.

In addition, an electronic medical records messaging system will be utilized for recruitment. A list of eligible patients will be identified using the inclusion criteria and ICD-10 codes. Once eligible patients are identified, permission will be obtained from the patients' clinicians to include them in the messaging outreach. With the clinicians' permission, the research team will send electronic medical record messages with study information.

Because this study requires long-term participation, contact information for the participant will be collected during the consent process. Prior to each visit, participants will receive reminder calls regarding the upcoming visit.

**Compensation**

Participants will receive compensation for participating in the study. For the completion of MR defecography, the participant will be compensated $100. For the completion of the surgery, the participant will be compensated $100. For

each of the post-operation visits completed (2 weeks, 2-12-24 months), the participant will be compensated $50. In total, the participant can be compensated up to $400.

Participants will be responsible for all costs that would normally incur as part of routine care, including costs related to the surgical treatment. There will be no charge associated with follow-up visits and post-operative ultrasounds.

# 6. Study Intervention

## 6.1 Study Intervention(s) Administration

### *6.1.1 Study Intervention Description*

**Transvaginal Sacrospinous Rectopexy Surgical Technique**

The posterior vaginal wall dissection is started with a horizontal incision in the mid-posterior vaginal wall. Dissection is carried down to the sacrospinous ligament (SSL) bluntly on each side. Sacrospinous ligament sutures are placed using a push-and catch suturing device (Capio Slim, Boston Scientific Corporation, USA) to deliver a single 0-polydiaxone suture (Monodek, Teleflex Medical OEM) into each ligament approximately 2-2.5 cm medial to the ipsilateral ischial spine (Figure 5). With one finger inside the rectum, the suture is passed through the lateral rectal ligament and rectal muscularis layer, as a two-bite running suture, at a point 7-8 cm cephalad to the anal verge. After tying down the knot on the first side, rectal suture placement is then performed on the contralateral side; this sequential suturing and tying down of left and right sided rectal suspensions allows for assessment and fine-tuning of the rectal suspension and avoidance of excess tension or stretching of the rectal wall. After suspension of the rectum bilaterally, three additional interrupted 0 polydiaxone sutures are used to reattach the midline posterior vaginal wall to the midline anterior rectal wall at the same level (7-8 cm cephalad from the anal verge); these sutures provide reinforcement and tension relief to the midline rectum between each lateral SSL suspension suture and serve to close a potential enterocele space.

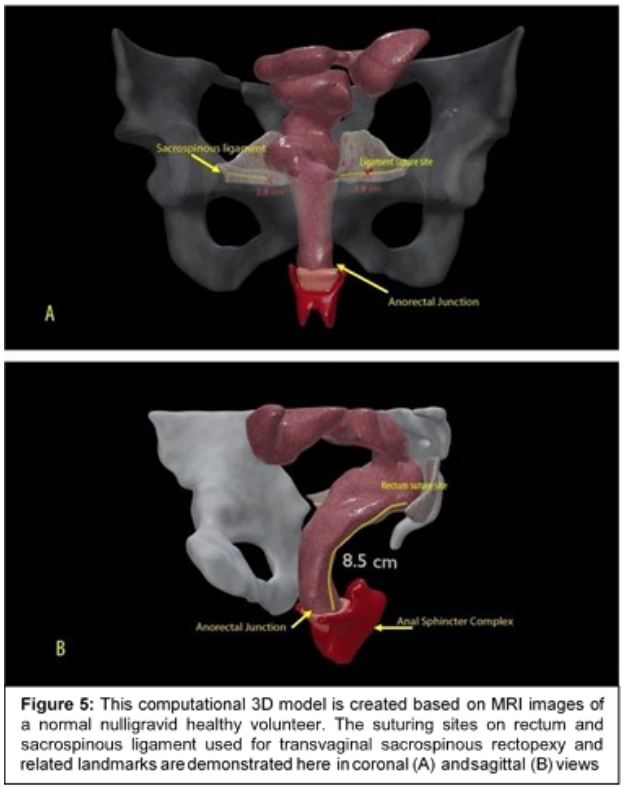



**Figure 5:** This computational 3D model is created based on MRI images of a normal nulligravid healthy volunteer. The suturing sites on rectum and sacrospinous ligament used for transvaginal sacrospinous rectopexy and related landmarks are demonstrated here in coronal (A) and sagittal (B) views

**Laparoscopic Abdominal Ventral Rectopexy Surgical Technique**

The surgery is performed under general anesthesia with patient in steep Trendelenburg position. Usually 4 ports are created. Supra-umbilical port is used as camera port. The rectosigmoid junction is identified and retracted to the left. A "J shaped" peritoneal incision is given extending from the sacral promontory to the anterior peritoneal reflection distally. Right hypogastric nerve and ureter are identified and safeguarded. With combined blunt and sharp dissection, a wide plane is developed in the Rectovaginal/rectovesical space. Any posterior rectal mobilization or lateral dissection is avoided at this stage. A strip of Prolene mesh (Ethicon Endosurgery, Blue Ash, Ohio, United States), trimmed to 3 cm × 17 cm, is prepared and inserted into the pelvic cavity. One end of mesh is fixed to the anterior surface of the distal most part of the rectum using polypropylene sutures. Similarly, it is fixed to the lateral borders of the rectum. Care is taken to avoid full thickness bite into the rectal wall in order to prevent mesh contamination. Finally, the proximal end of mesh is fixed to the sacral promontory using same sutures. Proximal traction on the rectum is avoided while fixing the mesh. The peritoneum is then re-approximated to completely cover the mesh.

**Conventional Vaginal Prolapse Surgery**

To minimize the number of confounding variables and reduce the complexity of analysis, types of conventional vaginal prolapse surgery will be limited to the following:

1. Vaginal prolapse repair surgery –
    a. Anterior vaginal repair surgery
    b. Posterior vaginal repair surgery
    c. Vault suspension
2. Abdominal prolapse repair surgery –
    a. Sacrocolpopexy
3. Tension-Free Vaginal Tape

#### *6.1.2 Dosing and Administration*

Not applicable.

### 6.2 Preparation/ Handling/ Storage/ Accountability

#### *6.2.1 Acquisition and Accountability*

At both study sites, all investigators will perform the dynamic pelvic ultrasound. MR defecography will be performed by trained personnel at each site. Transvaginal sacrospinous rectopexy will be performed by urogynecologists. Laparoscopic abdominal ventral rectopexy will be performed by colorectal surgeons.

Per Objective Structured Assessment of Technical Skill (OSATS), competency criteria for the novel transvaginal sacrospinous rectopexy will be performing three to five cases under the supervision of Dr. Ghazaleh Rostami Nia and/or Dr. Roger Goldberg until achieving the following milestone:

1. The surgeon was able to perform all aspects of the procedure safely and competently.

A second or third year urogynecology fellow or a second-year colorectal fellow will be able to assist in the surgeries under the direct supervision of investigators.

#### *6.2.2 Formulation, Appearance, Packaging, and Labeling*

Not applicable.

#### *6.2.3 Product Storage and Stability*

Not Applicable.

#### *6.2.4 Preparation*

Not Applicable.

### 6.3 Measures to Minimize Bias: Randomization and Blinding

**Randomization**

Participants will be assigned with equal probability to one of the two groups for each intervention TSR with and without CVPR versus LAVR with and without CVPR. Participants will be randomized after anesthesiologist clearance for both surgical approaches and prior to the preoperative visit. Every effort will be made to minimize the time between randomization and the surgery. Participant will have the opportunity to review the surgery detail with the surgeon during the preoperative visit. Separate randomization schedules will be generated by the DCC for each Clinical Site using a random permutated block design. The DCC will provide treatment allocations to the Clinical Sites using REDCap randomization feature.

**Masking**

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. Given the surgical procedure require a transvaginal or abdominal incision, it is clinically not possible to mask the participant or other research personnel. Every attempt will be made to keep the research coordinator blinded when assessing symptoms via questionnaires during follow up visits. The dynamic pelvic ultrasound image will be saved and re-evaluated in a blinded manner retrospectively to confirm the results of the initial reading.

### 6.4 Study Intervention Compliance

Surgeons will comply with randomization assignments to the extent possible. Variations will be documented as protocol deviation and justification for allowing clinical decision-making to overrule randomized treatment assignment will be documented. Protocol deviations will be reviewed by both the IRB and the Data Safety Monitoring Board (DSMB).

### 6.5 Concomitant Therapy

No additional surgical procedures will be performed at the same time as the research procedure described in this protocol. If any additional procedures, unanticipated or incidental, are performed for medical necessity, they will be documented as protocol deviation and described fully to the IRB and DSMB.

#### *6.5.1 Rescue Medicine*

Not applicable.

## 7. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

### 7.1 Discontinuation of Study Intervention

Incomplete MR imaging does not mean discontinuation from the study, and remaining study procedures can be completed as indicated by the study protocol. Patient can withdraw from the study before surgery.

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding, occurring or discovered after obtaining informed consent, will be reported as an adverse event (AE).

### 7.2 Participant Discontinuation/ Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive MRI or surgery for 3 months

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Participants who sign the informed consent form and are randomized but do not receive the study intervention may be

replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

### 7.3 Lost to Follow-Up

*A* participant will be considered lost to follow-up if she fails to return to any scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fail to return to the clinic for any required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 30 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 calls/messages and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8. Study Assessments and Procedures

### 8.1 Study Assessments

The surgical success or failure of will be measured by:

1. The degree of rectal hypermobility measured via dynamic pelvic ultrasound (i.e. compression ratio)

The criteria for surgical failure will be defined as follows:

1. A participant will be considered a surgical failure if:
    b. Rectal hypermobility with compression ratio more than 20% is detected via ultrasound.
2. Otherwise, a participant will be considered a surgical "success".

In addition to dynamic pelvic ultrasound, the following assessments will be performed:

1. Postoperative pain - Participants will complete the Pain Scale (67) and an assessment of pain medication use preoperatively, and then at 2 weeks, 2, 12 and 24 months postoperatively.
2. Postoperative functional activity level – Participants will complete the Activity Assessment Scale (68) which measures functional activity preoperatively and then at 2 weeks, 2 months, 12 months, and 24 months postoperatively.
3. Global improvement in bladder function – Participants will complete the Patient Global Impression of Improvement (69) at 2, 12 and 24 months after surgery.
4. Pelvic Floor Distress Inventory (PFDI) – Prolapse and colorectal symptoms as assessed by the POPDI and CRADI (short-term) and urinary and colorectal symptoms as assessed by the UDI and CRADI (long-term) subscales. Change in symptoms from 2, 12, and 24 months will also be assessed.
5. Quality of life measured by PFIQ (65), SF-36 (70), and EQ-5D (71) at 2, 12 and 24 months. The SF-36 will also be administered to a subset of participants 2 weeks post-operatively to allow validation of the Pain and Activity Assessment Scale.
6. Pelvic muscle strength as assessed by the Brink Scale 2, 12 and 24 months.

Based on measurements above, efficacy will be defined as follows:

1. Time to anatomic recurrence (time to failure)

    a. Urinary function: compare UDI scores (65) to assess urinary function generally and Hunskaar Incontinence Severity Index to assess the presence and severity of urinary incontinence specifically. Participants will also complete the Patients Global Impression of Improvement (PGI-I) (69) for impressions of bladder function.
    b. Bowel function: compare CRADI scores (65)
    c. Prolapse symptoms: compare POPDI scores (65)
2. Non-surgical treatment for pelvic floor disorders
    a. Pessary use for prolapse
    b. Stress urinary incontinence
    c. Urge urinary incontinence and other overactive bladder symptoms
    d. Voiding dysfunction
    e. Defecating dysfunction and/or fecal incontinence
3. QOL
    a. Global: compare SF-36 scores and sub-scales (73), EQ-5D. (71, 74)
    b. Disease-specific: compare urinary, bowel and prolapse scales of PFIQ score (65)
4. Participants' Perception of Motivation and Barriers to Continued Study Participation questionnaire

## 8.2 Safety and Other Assessments

Perioperative measures of morbidity include operative time (a risk factor for operative morbidity), estimated blood loss, and intra-operative and post-operative complications. Complications will be categorized using a modification of the Dindo Classification (77). Perioperative morbidity will be recorded at the completion of the surgery, at hospital discharge, and at the 2-week postoperative visit.

In addition, the following specific adverse events will be assessed and reported:

1. Intra-operative ureteral injury/obstruction (identified as no spill of urine from one or both ureteral orifices after prolonged observation (> 10 minutes) via cystoscopy; when indicated, other procedures may be used diagnostically or therapeutically, such as ureteral stent placement.)
2. Removal/replacement of vault suspension sutures to relieve intra-operative ureteral obstruction
3. Postoperative ureteral injury (delayed recognition)
4. Intra-operative neural injury (as determined by post-operative neuropathic pain or other neurologic sequelae) that was new onset: Neuropathic pain attributable to the vaginal vault suspension will be defined as "Acute-onset pain involving the buttock, groin and/or lower extremity, usually unilateral, occurring on the side or sides where vault suspension stitches have been placed and within one week of the index surgery requiring an alteration of routine postoperative care (e.g., nerve block, physical therapy, return to OR for suture removal, the addition of medications used to treat neuropathic pain such as anticonvulsants or tricyclic anti-depressants, or the increase or persistence of narcotic pain medication use beyond 14 days after surgery)."
5. Transfusion of blood products (e.g., whole blood, packed red blood cells, platelets)
6. Vaginal granulation tissue requiring treatment
7. Vaginal or perineal stricture (i.e., narrowing or scarring) prompting a treating physician to suggest or the participant to request treatment (surgical or non-surgical)
8. Rectal injury
9. Postoperative pain

## 8.3 Adverse Events and Serious Adverse Events

### *8.3.1 Definition of Adverse Events (AE)*

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

### *8.3.2 Definition of Serious Adverse Events (SAE)*

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### *8.3.3 Classification of an Adverse Event*

#### 8.3.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

#### 8.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

#### 8.3.3.3 Expectedness

Principal investigator and co-investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

### *8.3.4 Time Period and Frequency for Event Assessment and Follow-up*

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

PI and co-investigators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

### *8.3.5 Adverse Event Reporting*

Each investigator is responsible for reporting adverse events to the IRB at their institution, to the Data Coordinating Center (DCC), and to the NIH Program Official. The DCC will summarize the case and report it to the NIDDK program official and the Executive Secretary of the DSMB, who will determine whether it should be shared with the DSMB immediately or reported as part of the next scheduled report to the DSMB. The investigator must promptly inform the Ethics Board or IRB of adverse event per local reporting requirement. The Chair of the DSMB can convene an emergency meeting of the DSMB.

Every six months, or upon request of the NIDDK, the data coordinating center will summarize all adverse events (serious, expected, and unexpected) by treatment group in a report to the DSMB. In addition, the report will contain accrual, drop-out rates, and data quality metrics. The DSMB will summarize their findings to the NIH with a recommendation to continue the clinical trial, modify the trial, or terminate the trial.

### *8.3.6 Serious Adverse Event Reporting*

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal

relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor and the IRB of record.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center/DSMB/NIH and should be provided as soon as possible.

#### *8.3.7 Reporting Events to Participants*

Participants will be informed of AEs during an office visit soon after detecting AEs to discuss the problem and treatment options.

Participants will be informed of incidental findings soon after detecting them to discuss the problem and treatment options.

#### *8.3.8 Events of Special Interest*

Not applicable

#### *8.3.9 Reporting of Pregnancy*

Participants who become pregnant after entering the study will be withdrawn from the study and none of the study procedures will be performed.

### 8.4 Unanticipated Problems

#### *8.4.1 Definition of Unanticipated Problems (UP)*

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

#### *8.4.2 Unanticipated Problem Reporting*

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB), the NIDDK program official, and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 30 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 30 days of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

#### *8.4.3 Reporting Unanticipated Problems to Participants*

Participants will be informed of UPs during an office soon after detecting AEs to discuss the problem and treatment options.

## 9. Statistical Considerations

### 9.1 Statistical Hypothesis

**Primary Aim**

We anticipate that patients who received transvaginal sacrospinous rectopexy (TSR) will show significantly greater surgical success comparing to laparoscopic abdominal ventral rectopexy (LAVR) group, and this change is expected to remain at 24 months. TSR will result in superior outcomes over LAVR.

**Secondary Aim**

We anticipate that rectal hypermobility can be detected via both dynamic imaging, ultrasound and MR defecography. We expect the degree of a rectal support defect will correlate well between the two imaging modalities and with symptom severity.

### 9.2 Sample Size Determination

Based on our preliminary studies in literature (83-87), we assume an anatomic success rate in LAVR group is about 70% at 24 months. The investigators believe that a difference in success rates less than 25% will not change clinical practice, but also that the sample size should be large enough so that an observed difference in success rates of 20% would be significant; i.e., an inability to differentiate between the procedures will require an observed difference that is less than 20%.

The study will be individually randomized group-treatment trial (IRGT), which patients are randomized to surgical interventions through a common surgeon (88-90). There will be three surgeons performing each surgical treatment. The number of surgeons and patients will be the same in each clinical site. We anticipate an average of 16 individually randomized patients per surgeon in each treatment group. Outcomes for patients treated by the same surgeon tend to be more similar. We assume minimal variability, estimating a small intraclass correlation coefficient (ICC) of 0.01. The table below illustrates power to detect at least 23% difference between treatment groups with varying assumptions on ICC and dropout rates. A total of 96 patients (48 patients per group) would yield 86% power to differentiate between anatomical success rates of 70% and 93% assuming an ICC of 0.01 and a two-sided 5% level of significance. Projecting a 20% dropout/loss to follow up rate over 2 years, we anticipate recruiting and up to 120 total patients.

| ICC | % Dropout | Total patients | Average patients per surgeon | Power |
|---|---|---|---|---|
| 0.01 | 0 | 120 | 20 | 92% |
| | 10 | 108 | 18 | 90% |
| | 20 | 96 | 16 | 86% |
| 0.02 | 0 | 120 | 20 | 90% |
| | 10 | 108 | 18 | 87% |
| | 20 | 96 | 16 | 83% |
| 0.05 | 0 | 120 | 20 | 82% |
| | 10 | 108 | 18 | 79% |
| | 20 | 96 | 16 | 76% |

Due to concerns that ICC is higher than expected or dropout rate is higher than 20% toward the end of 2-year follow-up, we calculated the sample size that would be needed for 87% power to differentiate between anatomical success rates of 70% and 95% (a difference of 25%) in treatment groups with a two-sided 5% level of significance. The required sample size is 39 per group, or 78 total patients.

## 9.3 Populations for Analyses

**Modified Intent-to-treat (mITT) Population**
The mITT population will include all randomized participants who received at least one post-op visit. Participants will be analyzed according to their randomized treatment assignment, regardless of the treatment actually received.

**Safety Population**
The safety population will include all participants who received any study treatment. All safety analyses will use the safety population. Participants will be analyzed according to the treatment they actually received, regardless of the treatment assigned.

**Per-protocol (PP) Population**
The PP population is a subset of the ITT population who completed the study without any major protocol violations. Analyses will exclude the following randomized participants: (83) those who did not receive TSR/LAVR surgery as planned; (84) those who died within 12 months of surgery and were not assessed on the primary outcome before their death; (85) those who withdrew from study and withdrew consent for use of their data.

**Full Analysis Set (FAS)**
The FAS will include all randomized participants who receive any study treatment and have at least one assessment since the baseline visit. Participants will be analyzed in their randomized treatment assignment, regardless of the treatment actually received.

## 9.4 Statistical Analyses

### *9.4.1 General Approach*

After examining for outliers and missing values, the distributions of continuous measures will be examined. When necessary, the data may be transformed or non-parametric tests will be used. Baseline measures will be compared between the treatment groups to identify imbalances. All statistical analyses will be performed using SAS 9.4 (SAS Institute Inc., Cary, NC) with two-sided 5% level of significance.

Implementation of the planned statistical analysis will be described in the Statistical Analysis Plan (SAP) prior to locking the database.

### *9.4.2 Analysis of the Primary Efficacy Endpoint(s)*

**Anatomical Surgical Outcome**
The primary endpoint for the surgical treatment is dichotomous: success or failure at 24 months after surgery. The primary outcome measure uses the rectal compression ratio at 24 months unless there has been retreatment at an earlier time. When there is retreatment, or when the 24-month ultrasound results and POPQ results are missing and the last observed measurements were consistent with the definition of failure, then the results at 24 months will be imputed to be a failure. A sensitivity analysis will be performed to study the effect on the primary endpoint of different methods of handling dropouts and missing data. It will be conducted by assuming various values for the imputed outcomes and comparing the results under those assumptions to the results of the primary analysis.

Cochran-Mantel-Haenszel (CMH) test will be used to compare between surgical treatments adjusting for stratification factor. In addition, Generalized linear mixed-effects models (GLMMs) will be performed to yield an effect estimate of conditional on surgeon. Demographics and other characteristics at baseline (treatment group, age, BMI, menopausal status, parity, duration and severity of ODS) will be included. Surgeon will be included as a random effect to account for

correlation between outcomes of patients treated by the same surgeon. Adjusted odds ratios (ORs) will be presented with 95% confidence intervals (CIs).

### *9.4.3 Analysis of the Secondary Endpoint(s)*

**Subjective Surgical Outcome**

The secondary endpoint is the presence of OD symptoms (yes/no) at 24 months after surgery. Questionnaires that assess the presence and severity of OD symptoms include pain/activity assessment scale, global improvement in bladder function, prolapse and colorectal symptoms as assessed by POPDI, CRADI, UDI, quality of life by PFIQ, SF-36, EQ-5D, and pelvic muscle strength measured by Brink Scale. Differences between surgical treatments will be analyzed using generalized linear mixed-effects models, as described for the primary endpoint. However, imputation of missing values will not be done for secondary measures.

**Validation**

There will be two forms of validation: statistical and radiological. For statistical validation, we expect to see a significant and positive correlation between measurements of the Compression ratio between the two modalities. However, since the Compression ratio as measured via MR defecography is not used clinically to diagnose abnormalities in rectal support (rectal prolapse or rectal intussusception), this does not validate the use of ultrasound for diagnostic purposes. Thus, radiological validation will be performed where the Compression ratio is also correlated with a radiologist's diagnosis of an abnormality in rectal support.

### *9.4.4 Safety Analysis*

Any endpoints that relate to safety will be analyzed using methods previously described.

All adverse events collected will be coded. Events will be summarized cumulatively through the following time points: 2 weeks, 2 months, 12 months, and 24 months postoperatively. Severity and frequency of AEs will be presented. In addition, the frequency and percentage of participants who had a Serious AE (SAE) or a related AE will be tabulated separately.

### *9.4.5 Baseline Descriptive Statistics*

A summary table with descriptive statistics will be generated for baseline characteristics, including demographics and laboratory measurements based on the ITT population. Baseline characteristics will be presented by intervention groups in a table, but no formal statistical hypothesis testing will be performed. Continuous variables will be summarized using mean with standard deviation or median with interquartile range. Categorical variables will be summarized using frequency and percentage.

Baseline characteristics include demographics, medical history, surgical history, physical exam, pelvic ultrasound, MR defecography, POPQ, PFDI, Pain Scale, Assessment of pain medication use, and Activity assessment scale.

### *9.4.6 Planned Interim Analysis*

No interim analyses are planned.

### *9.4.7 Sub-Group Analyses*

Subgroup analyses of the primary efficacy endpoint will be conducted for demographics (e.g., age, BMI, menopausal status, parity), duration and severity of ODS, and concomitant surgery. Descriptive statistics will be presented stratified by aforementioned variables. Data will be analyzed using the same method as described for the primary efficacy endpoint.

### *9.4.8 Tabulation of Individual Participant Data*

Not Applicable

#### *9.4.9 Exploratory Analyses*

We will investigate the correlation between measurements of compression ratio between two modalities and present a cut-off for these measurements relevant to presence of OD symptoms in our secondary endpoints. For an optimal cut-off, the sensitivity and specificity will be calculated based on receiver operating characteristic (ROC) curve.

We will develop and validate a computational finite element model and statistical shape modeling approach to describe the mechanics of normal defecation and the role of rectal and vaginal support deficiencies in causing OD symptoms.

# 10. Supporting Documentation and Operational Considerations

## 10.1 Regulatory, Ethical, and Study Oversight Considerations

### *10.1.1 Informed Consent Process*

#### 10.1.1.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The risks and benefits of each surgical approach including the risk of prolapse recurrences will be discussed during consent and pre-operative visits. During the pre-operative visit, which will occur after anesthesiologist clearance and randomization, participants will have the opportunity to review the surgery details with the surgeon. Participants randomized to laparoscopic ventral rectopexy will complete the preoperative visit with a colorectal surgeon. Those assigned to transvaginal sacrospinous rectopexy will complete the preoperative visit with a urogynecologist. Every effort will be made to minimize the time between randomization and the surgery. Surgical failure resulting from either surgical approach will be addressed per current guidelines for surgical failures which include symptoms assessment for conservative or surgical management.

#### 10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. Written informed consent will be obtained from all study participants. Consent will be obtained by study-related personnel who are knowledgeable of the study and who have training in the consent process and in the protection of human participants. No study-related procedures (interview, chart abstraction, research ultrasound studies, questionnaires) will be undertaken before a signed consent form has been completed. During the process of obtaining informed consent, potential participants will have the nature of the study, specimen collection, data collection procedures, study ultrasound procedures, the importance of compliance to study procedures, and the potential risks and benefits explained to them. Potential participants will be told that there is no obligation to participate, that there will be no penalty for declining to participate and that their treatment will not be compromised if they choose not to participate or cease participation at any time. Ample time will be provided for each potential participant to read and understand the consent form and to ask questions. The potential participant will be able to take the consent form/informational form home to discuss participation with family/friends/personal physician. A separate visit will be scheduled for the potential participant to return to the clinic to ask questions and sign the consent form with the research coordinator or research assistant. A participant who consents to the study will be given a copy of the signed consent form for their personal records. A copy will be placed in their medical record. The original signed copy will be kept in a locked file at the clinical site with other confidential information on the participant.

### *10.1.2 Study Discontinuation and Closure*

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

### *10.1.3 Confidentiality and Privacy*

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Data Coordinating Center.

### *10.1.4 Future use of Stored Specimen and Data*

Data collected for this study will be analyzed and stored at the Data Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the ClincialTrials.gov for use by other researchers including those outside of the study.

When the study is completed, access to study data will be provided through the ClinicalTrials.gov.

### *10.1.5 Key Roles and Study Governance*

| **Principal Investigator** |
| --- |
| *Ghazaleh Rostami Nia, MD, MSc, Director of Research Division of Urogynecology, NorthShore University HealthSystem, Clinical Assistant Professor, University of Chicago* |

| |
|---|
| *Pritzker School of Medicine, Female Pelvic Medicine and Reconstructive Surgery Division, Department of Obstetrics and Gynecology* |
| *NorthShore University HealthSystem* |
| *9650 Gross Point Rd. Suite 3900 Skokie, IL 60076* |
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| |

The Clinical Centers:
NorthShore University HealthSystem – Skokie, IL; PI Ghazaleh Rostami Nia, MD, MSc, Co-I Roger Goldberg, MD, MPH
Weill Cornell Medical Center- New York Presbyterian – New York, NY; PI Tirsit Shiferaw Asfaw, MD, Co-I Jeffrey Wilson, MD, Co-I Kelly Garrett, MD

Biostatistician:
NorthShore University HealthSystem – Skokie, IL; Cecilia Chang, MS

Bioengineer:
University of Pittsburg - Pittsburgh, PA; Steven Abramowitch, PhD

The Data Coordinating Center:
NorthShore University HealthSystem – Skokie, IL; PI Ghazaleh Rostami Nia, MD, MSc

The NIDDK Program Director:
Dana K. Andersen, M.D.

### *10.1.6 Safety Oversight*

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB), chartered by the NIDDK, composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NIDDK. The NIDDK program official will communicate the DSMB's recommendations to the PI. The PI is responsible for providing the DSMB documentation to the IRB of record and other study personnel as appropriate.

### *10.1.7 Clinical Monitoring*

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Study PI and co-PI at each site will conduct the clinical site monitoring every 20 participants recruited with comprehensive review of all 20 participants' data.

### *10.1.8 Quality Assurance and Quality Control*

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following the protocol, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

### *10.1.9 Data Handling and Record Keeping*

#### 10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data collected from the worksheet and participants' Electronic Medical Record System will be recorded and stored in REDCap, a secure, password-protected interspace. Hard copies of the study visit worksheet will be kept locked in office with limited access. The principal investigator, co-investigator, and research staff will have access to the REDCap. The research coordinator of the Data Coordinating Center will be responsible for creating the REDCap template to be distributed to the collaborating center for consistency in data collection. Research coordinators of each site will be responsible for inputting data into the REDCap. The principal investigator and co-investigator will be responsible for reviewing the data inputted in the REDCap for accuracy.

#### 10.1.9.2 Study Record Retention

Study documents should be retained for 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

### *10.1.10 Protocol Deviation*

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 15 working days of identification of the protocol deviation, or within 15 days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NIDDK Program Official and Data Coordinating Center. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

#### *10.1.11 Publication and Data Sharing Policy*

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting principal investigator of the study.

#### *10.1.12 Conflict of Interest Policy*

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDDK has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

### 10.2 Additional Considerations

Not applicable.

### 10.3 Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| CFR | Code of Federal Regulations |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRADI | Colo-Rectal Anal Distress Inventory |
| CRF | Case Report Form |
| CVPS | conventional vaginal prolapse surgery |
| DCC | Data Coordinating Center |
| DSMB | Data and Safety Monitoring Board |
| EQ-5D | EuroQol-5 Dimension |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Conference on Harmonisation |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |

| | |
|---|---|
| LAVR | laparoscopic abdominal ventral rectopexy |
| MR | Magnetic Resonance |
| NCT | National Clinical Trial |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| OS | obstructed defecation |
| PFDI | Pelvic Floor Distress Inventory Questionnaire |
| PFIQ | Pelvic Floor Impact Questionnaire |
| PI | Principal Investigator |
| POP | Pelvic Organ Prolapse |
| POPDI | Pelvic Organ Prolapse Distress Inventory |
| POPQ | Pelvic Organ Prolapse Quantification system |
| QC | Quality Control |
| QOL | Quality of Life |
| RF | Radiofrequency |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SF-36 | 36-item short-form |
| TSR | Transvaginal sacrospinous rectopexy |
| SOA | Schedule of Activities |
| UDI | Urinary Distress Index |
| UP | Unanticipated Problem |
| US | United States |

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## 12. Appendices

Appendix A – SOP: MR Defecography
Appendix B – SOP: Dynamic Pelvic Ultrasound
Appendix C – SOP: Surgical Procedures
Appendix D – SOP: Study Assessments and Measurements
Appendix E – Schedule of Forms

PROD Trial
Research Standard Operating Procedure

| SOP TITLE: MR Defecography | Version # 1 |
|---|---|
| SOP NUMBER: PROD_SOP_1 | Page 40 of 50 |

**PURPOSE:**
To describe expectations for completing MR Defecography for the PROD Trial.

**PERSONNEL RESPONSIBLE:**
Trained personnel at each study site.

**PROCEDURES:**

1. MR imaging will be in the supine position with hips and knees bent at 45° using a closed-configuration 1.5T magnet (Siemens, Magnetom Avanto) and a Synergy body phased-array coil.
    a. As with routine dynamic pelvic floor MRI examinations performed at NorthShore University HealthSystem, intravenous contrast will not be used.
    b. No bowel preparation or intraluminal contrast material will be administered.
2. Subjects will be instructed to empty their bladder three hours before the examination to result in a moderately full urinary bladder during MRI.
3. Static multiplanar images of the pelvis will be acquired for anatomic evaluation using a 3-mm slice thickness with a 0-mm gap, for sagittal and axial T2-weighted sequences (echo time, 105 milliseconds; repetition time, 3000 milliseconds).
    a. These will be used to collect anatomical geometries for use in modeling.
4. The rectum will then be filled with 60 mL of ultrasound gel (1% Gd-DTPA-GEL-Mixture).
5. The pelvis will be visualized in three planes (transversal, coronal, sagittal, T1 and T2) to find the appropriate sagittal plane in which all relevant pelvic floor organs could be acquired during defecation.
6. The sequence will take ~36s at a frequency of one shot per 1.1 s (True Fast Imaging with Steady State Precession; TR: 1.8 ms, TE: 1.01 ms).
7. Slice thickness will be 6 mm (field of view: 300 mm x 270 mm, image matrix: 256 x 256).
8. During the examination, patients will be instructed via headphones to first relax and then to perform a squeeze maneuver.
    a. This will be followed by instructions to perform straining and evacuation maneuvers with the goal of emptying the rectum as completely as possible.
9. For measurements, three anatomic measurements relating to rectal support will be recorded at rest, and then also at the moment of maximum evacuation, which will be defined as the image in which the posterior cul de sac makes its closest approach to the anorectal junction.
    a. The first measurement will be the straight distance between the posterior cul de sac and anorectal junction.
    b. The second measurement will be the perpendicular distance between the cul de sac and the pubo-coccygeal line.
    c. The third measurement will be the perpendicular distance between the anorectal junction and the pubo-coccygeal line.
10. The relative change in length of the straight distance between the posterior cul de sac and the anorectal junction (CDS to ARJ) as observed on MR defecography will be used to define a compression ratio, which will

again be calculated as a percentage using the following formula:  Compression ratio = 100 * (CDS to ARJ length at rest – CDS to ARJ septum length at evacuate) / CDS to ARJ length at rest.

PROD Trial
Research Standard Operating Procedure

| SOP TITLE: Dynamic Pelvic Ultrasound | Version # 1 |
|---|---|
| SOP NUMBER: PROD_SOP_2 | Page 42 of 50 |

**PURPOSE:**
To describe expectations for completing Dynamic Pelvic Ultrasound for the PROD Trial.

**PERSONNEL RESPONSIBLE:**
Trained investigators of the PROD Trial.

**PROCEDURES:**

- The ultrasound procedure will be performed and read by trained investigators, including Drs. Ghazaleh Rostami Nia and Roger Goldberg at NorthShore University HealthSystem and Drs. Tirsit Shiferaw Asfaw and Kelly Garrett at Weill Cornell Medical Center- New York Presbyterian.
    - The dynamic pelvic ultrasound image will be saved and re-evaluated in a blinded manner retrospectively to confirm the results of the initial reading.
- The competency criteria for the ultrasound procedure will be performing three to five cases under the supervision of Dr. Ghazaleh Rostami Nia and/or Dr. Roger Goldberg until achieving the following milestone:
    - The physician was able to perform all aspects of the procedure safely and competently.
- The principal investigator of the study, Dr. Ghazaleh Rostami Nia, will review the data quality of the ultrasound procedures for the first ten ultrasounds completed.

**Dynamic Pelvic Ultrasound:**

1. Imaging will be obtained at the time of the study visit using:
    a. BK Medical bk3000 with
    b. 3D X14L4 (9038) Endocavity Transducer (frequency range: 14-4 MHz, focal range: 3-60 mm)
2. All ultrasound studies will be performed in the office setting with the patient in the dorsal lithotomy position, with hips flexed and abducted.
3. No preparation will be required, and no rectal or vaginal contrast will be used.
4. Patients will be instructed to arrive to the office with a partially full bladder, and to avoid excessive pressure on surrounding structures that might distort the anatomy, the probe will be inserted into the vagina in a neutral position.
5. 360 degree endovaginal ultrasound volumes and dynamic ultrasound videos will be saved for further analysis.
6. For measurements, the distance between the posterior cul de sac and anorectal junction (“rectovaginal septum length”) will be measured both at rest and during Valsalva straining efforts using a dynamic imaging protocol in the mid-sagittal plane, allowing posterior compartment structures to be visualized. It should be noted that for Valsalva straining efforts, patients will be instructed to relax their pelvic floor while increasing intra-abdominal pressure. All images will include the cul de sac apically and the levator plate/anorectal junction caudally in order to standardize framing of the anatomy, and the dynamic recording will be started with the patient at rest and captured for 5 seconds of Valsalva straining (see Figure 1 top left & right).

a. “Compression ratio” will be calculated as a means to quantify the relative change in length of the rectovaginal septum (RVS), in other words the degree of hypermobility / sliding rectum, and is expressed as a percentage using the following formula: $CR$ = (RVSr – RVSv)/ RVSR * 100 where RVSr (Rectovaginal Septum) and RVSv represent the RVS length at rest and Valsalva.

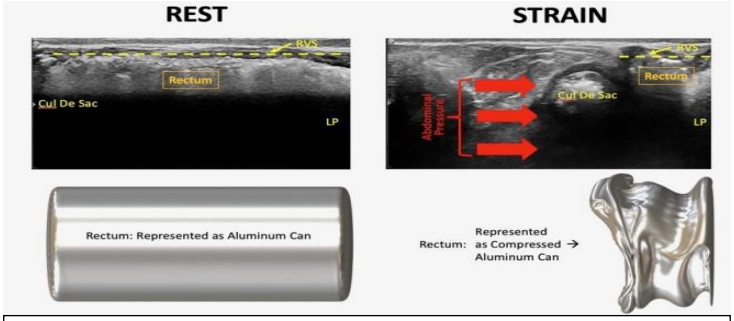


**Figure 1:** 2D dynamic endovaginal posterior compartment ultrasound of a patient with obstructed defecation symptoms at rest (left image) and at strain (right image). Rendering of an aluminum can is used to illustrate the concept of the rectal compression seen above. LP: Levator Plate, RVS: Rectovaginal Septum

PROD Trial
Research Standard Operating Procedure

| SOP TITLE: Surgical Procedures | Version # 1 |
|---|---|
| SOP NUMBER: PROD_SOP_3 | Page 44 of 50 |

**PURPOSE:**
To describe expectations for completing surgical procedures (Transvaginal Sacrospinous Rectopexy and Laparoscopic Abdominal Ventral Rectopexy) for the PROD Trial.

**PERSONNEL RESPONSIBLE:**
Investigators performing surgical procedures of the PROD Trial.

Per Objective Structured Assessment of Technical Skill (OSATS), competency criteria for the novel transvaginal sacrospinous rectopexy will be performing three to five cases under the supervision of investigator at NorthShore University HealthSystem until achieving the following milestone:

2. The surgeon was able to perform all aspects of the procedure safely and competently with no or minimal need for help, or in the context of an unexpectedly difficult case, may have needed more assistance for the more difficult aspects of the procedure.

A second or third year urogynecology fellow or a second-year colorectal fellow will be able to assist in the surgeries under the direct supervision of investigators.

**PROCEDURES:**

**Laparoscopic Abdominal Ventral Rectopexy Surgical Technique**

1. The surgery is performed under general anesthesia with patient in steep Trendelenburg position.
2. Usually 4 ports are created. Supra-umbilical port is used as camera port. The rectosigmoid junction is identified and retracted to the left.
3. A “J shaped” peritoneal incision is given extending from the sacral promontory to the anterior peritoneal reflection distally.
4. Right hypogastric nerve and ureter are identified and safeguarded. With combined blunt and sharp dissection, a wide plane is developed in the Rectovaginal/rectovesical space.
5. Any posterior rectal mobilization or lateral dissection is avoided at this stage. A strip of Prolene mesh (Ethicon Endosurgery, Blue Ash, Ohio, United States), trimmed to 3 cm × 17 cm, is prepared and inserted into the pelvic cavity.
6. One end of mesh is fixed to the anterior surface of the distal most part of the rectum using polypropylene sutures.
7. Similarly, it is fixed to the lateral borders of the rectum.
8. Care is taken to avoid full thickness bite into the rectal wall in order to prevent mesh contamination.
9. Finally, the proximal end of mesh is fixed to the sacral promontory using same sutures.
10. Proximal traction on the rectum is avoided while fixing the mesh.
11. The peritoneum is then re-approximated to completely cover the mesh.

**Transvaginal Sacrospinous Rectopexy Surgical Technique**

1. The posterior vaginal wall dissection is started with a horizontal incision in the mid-posterior vaginal wall.

2. Dissection is carried down to the sacrospinous ligament (SSL) bluntly on each side. Sacrospinous ligament sutures are placed using a push-and catch suturing device (Capio Slim, Boston Scientific Corporation, USA) to deliver a single 0-polydiaxone suture (Monodek, Teleflex Medical OEM) into each ligament approximately 2-2.5 cm medial to the ipsilateral ischial spine (Figure 5).
3. With one finger inside the rectum, the suture is passed through the lateral rectal ligament and rectal muscularis layer, as a two-bite running suture, at a point 7-8 cm cephalad to the anal verge.
4. After tying down the knot on the first side, rectal suture placement is then performed on the contralateral side; this sequential suturing and tying down of left and right sided rectal suspensions allows for assessment and fine-tuning of the rectal suspension and avoidance of excess tension or stretching of the rectal wall.
5. After suspension of the rectum bilaterally, three additional interrupted 0 polydiaxone sutures are used to reattach the midline posterior vaginal wall to the midline anterior rectal wall at the same level (7-8 cm cephalad from the anal verge); these sutures provide reinforcement and tension relief to the midline rectum between each lateral SSL suspension suture and serve to close a potential enterocele space.

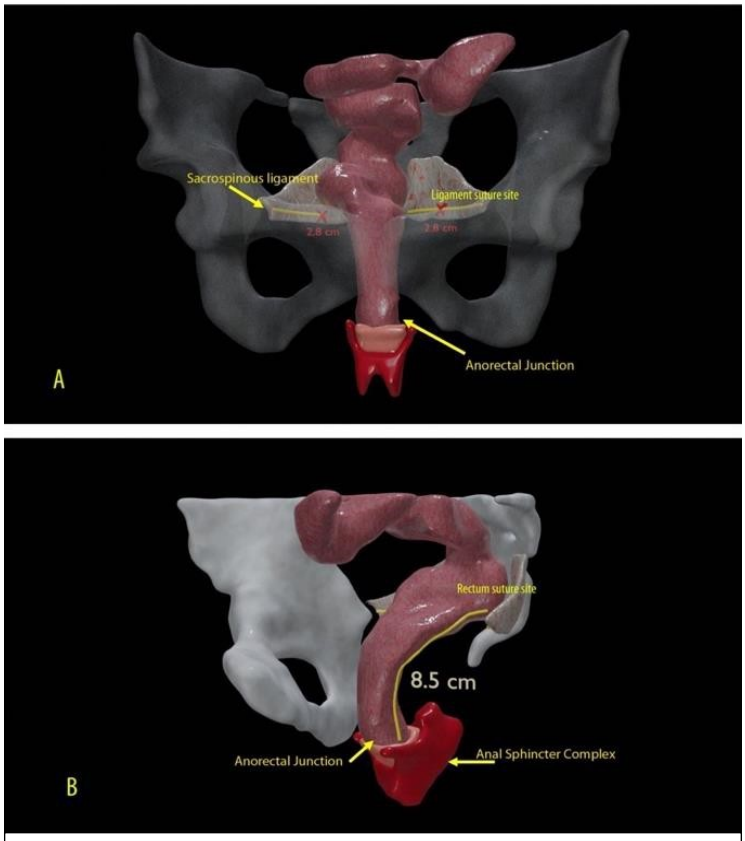


**Figure 5:** This computational 3D model is created based on MRI images of a normal nulligravid healthy volunteer. The suturing sites on rectum and sacrospinous ligament used for transvaginal sacrospinous rectopexy and related landmarks are demonstrated here in coronal (A) and sagittal (B) views

PROD Trial
Research Standard Operating Procedure

| SOP TITLE: Study Assessments and Measurements | Version # 1 |
|---|---|
| SOP NUMBER: PROD_SOP_4 | Page 46 of 50 |

**PURPOSE:**
To describe expectations for completing study assessments and measurements for the PROD Trial.

**PERSONNEL RESPONSIBLE:**
All investigators and research coordinators of the PROD Trial.

**PROCEDURES:**

**Pelvic Organ Prolapse Quantification (POP-Q) Assessment**
POP-Q assessment will be completed by investigators during screening, 2-month, 12-month, and 24-month post-operative appointments. Participants will be asked to empty the bladder and if feasible empty the rectum. The participant is then positioned where the utmost magnitude of the prolapse is shown and can be confirmed by the patient. A Sim's speculum can be used to draw back the anterior and posterior vaginal walls during the examination. The plane of the hymen will be defined as zero and all measures in centimeters above/proximal (negative number) or below /distal (positive number) to the hymen. All measurements should be recorded to the nearest half-centimeter (i.e., 0.0 or 0.5). The measurement parameters will include six distinct locations:

1. **Point Aa** is at the midline of the anterior vaginal wall. Where no prolapse is present this location is 3cm up from the hymen (merely interior to the vaginal opening). Parameters from the hymen can be -3cm indicating no anterior vaginal prolapse or +3cm, which is a full prolapse.
2. **Point Ba** refers to the most distal portion of the remaining upper anterior side of the vaginal wall.
3. **Point C** is the lowest edge of the cervix or the vaginal cuff (i.e. hysterectomy scar).
4. **Point D** is the topmost point of the posterior vaginal wall.
5. **Point Ap** is located midline of the posterior vaginal wall 3cm proximal to the hymen. The parameters for this point can range from -3cm to +3cm relative to hymen.
6. **Point Bp** refers to the most distal portion of the remaining upper posterior side of the vaginal wall. Its location can range from -3 to +6 or +7 in severe cases.

Furthermore, three anatomical markers can be examined:

1. **GH** is the 'Genital hiatus' that records the length from the urethral opening to the posterior vaginal opening/ hymen.
2. **PB** is the 'perineal body' and is recorded from the posterior aspect of the hymen to the mid-anal opening.
3. **TVL** refers to the 'total vaginal length' measured from the hymen to the most distal point. Knowing this allows the depth of prolapse to be assessed and reassessed post-surgical repair.

The position of the six distinct locations is measured during a maximum Valsalva or cough with regard to the hymen. The measurement of TVL should be recorded at rest when the prolapse is decreased.

**Brink Scale**
Brink assessment will be completed by investigators during 2-month, 12-month, and 24-month post-operative appointments. Participants will be asked to be in the dorsal lithotomy position. The Brink assessment will be performed by placing 1 or 2 lubricated fingers vaginally during a single Kegel contraction. The brink scale consists of 3 separate 4-point rating scales for vaginal pressure, vertical displacement of examiner's fingers, and duration of contraction. The pressure felt by examining fingers is rated 1 ("no response"), 2 ("weak squeeze"), 3 ("moderate squeeze"), or 4 ("strong squeeze"). The vertical displacement is rated 1 ("none"), 2 ("finger base moves anteriorly"), 3 ("whole length of fingers move anteriorly"), or 4 ("whole fingers move anteriorly, are gripped and pulled in"). Duration of contraction (in seconds)

is timed and scored 1 (“none”), 2 (“<1 second”), 3 (“1–3 seconds”), or 4 (“>3 seconds”). Ratings are summed to obtain total scores, with a possible range of scores of 3 to 12.

**Bowel Habit**
Bowel habits will be assessed by the research personnel during screening, 2-month, 12-month, and 24-month post-operative appointments. The participant will be asked about the average frequency of bowel movements in the past 3 months (more than 3 times per day, 2 to 3 times per day, once per day, 2 to 4 times per week, or less than once a week). Then the participant will be asked to identify one of the seven stool types that applies to their usual bowel movement in the past 3 months.

**Pelvic Floor Distress Inventory (PFDI) Assessment**
PFDI assessment will be completed by the research personnel during screening, 2-month, 12-month, and 24-month post-operative appointments. PFDI has 20 items and 3 scales of symptoms. All items use the format with a response scale from 0 (symptom is not present) to 4 (symptom is present quite a lot). The mean value of all the answered items within each scale will be multiplied by 25 to obtain the scale score (range 0 to 100). Missing items are dealt with by using the mean from answered items only. The PFDI summary score will be obtained by adding the scores from the 3 scales together (range 0 to 300).

**Pain Scale and Pain Medication Use**
Pain scale and pain medication use assessment will be completed by the research personnel during screening, 2-week, 2-month, 12-month, and 24-month post-operative appointments. Participants will be asked to rate the average amount of pain within the past 24 hours while at rest, with normal activities, with exercise, and worst pain of the today. All items use the format with a response scale from 0 (no pain sensation) to 10 (most intense pain imaginable). Then the participant will be asked if they are currently taking narcotic pain medication.

**Activity Scale**
Activity scale will be completed by the research personnel during screening, 2-week, 2-month, 12-month, and 24-month post-operative appointments. Participants will be presented with 13 activities in which they will be asked to rate how difficult it was for them to perform them in the past 24 hours. The rating will be 1 (no difficulty), 2 (a little difficulty), 3 (some difficulty), 4 (a lot of difficulty), 5 (not able to do it), and 6 (did not do it for other reasons). Then, participants will be asked 5 additional questions regarding activity in the past month.

**Impression of Improvement**
Impression of improvement assessment will be completed by the research personnel during 2-month, 12-month, and 24-month post-operative appointments. Participants will be asked to indicate a number that best describes their current post-operative condition in comparison to how it was pre-operatively. The rating will be 1 (very much better), 2 (much better), 3 (a little better), 4 (no change), 5 (a little worse), 6 (much worse), and 7 (very much worse).

**Pelvic Floor Impact Questionniare (PFIQ)**
PFDI assessment will be completed by research personnel during 2-month, 12-month, and 24-month post-operative appointments. The PFIQ-7 consists of 7 questions that need to be answered 3 times each considering symptoms related to the bladder or urine, vagina or pelvis, and bowel or rectum and its effect on function, social health, and mental health in the past 3 months. The responses for each question range from 0 (not at all) to 3 (quite a bit). To get scale scores, the mean of each of the 3 scales is individually calculated, which ranges from 0-3. This number is then multiplied by 100 and then divided by 3. The scale scores are then added together to get the total PFIQ-7 score, which ranges from 0-300.

**Short Form (SF) - 36**
SF-36 assessment will be completed by the research personnel during 2-week, 2-month, 12-month, and 24-month post-operative appointments. SF-36 is comprised of 36 questions that cover eight domains of health: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue),

and general health perceptions. Participants will be asked to fill out the questionnaire by themselves. Then the research personnel will input the questionnaire results into an online scoring calculator (https://orthotoolkit.com/sf-36/).

**EuroQol-5 Dimension (EQ-5D)**

EQ-5D assessment will be completed by the research personnel during 2-month, 12-month, and 24-month post-operative appointments. The EQ-5D covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to. There are 3,125 possible health states defined by combining one level from each dimension, ranging from 11111 (full health) to 55555 (worst health).

## APPENDIX E – Schedule of Forms

| | Screening Appt | Initial Appt +/- 30 days | MRI Appt +/- 30 days | Anesthesia Clearance | Randomization | Pre-op | Day of Surgery | 2 wk PO +/- 5 days | 2 m PO +/- 10 days | 12 m PO +/- 10 days | 24 m PO +/- 30 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Form 01 Eligibility | | X | | | | | | | | | |
| Form 02 Demographics | | X | | | | | | | | | |
| Form 03 Medical History | | X | | | | | | | | | |
| Form 04 Baseline PE | X | | | | | | | | | | |
| Form 05 Follow-up PE | | | | | | | | | X | X | X |
| Form 06 Surgeon's report | | | | | | | X | | | | |
| Form 07 2 week post-op visit | | | | | | | | X | | | |
| Form 08 Activity Assessment | X | | | | | | | X | X | X | X |
| Form 09 Pain Scale | X | | | | | | | X | X | X | X |
| Form 10 EQ-5D | | | | | | | | | X | X | X |
| Form 11 SF-36 | | | | | | | | X | X | X | X |
| Form 12 PFIQ | | | | | | | | | X | X | X |
| Form 13 PFDI | X | | | | | | | | X | X | X |
| Form 14 Global Impression | | | | | | | | | X | X | X |
| Form 15 Bowel Habit | X | | | | | | | X | X | X | X |
| Form 16 Research Participation | | | | | | | | | | | X |
| Form 17 Adverse Event | | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) |
| Form 18 Unanticipated Problem | | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) |
| Form 19 Protocol Deviation | | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) |
| Form 20 Study Exit | | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) | X (if applicable) |