A Randomized Trial Comparing Continence Pessary to Continence Device (Poise Impressa®) for Stress Incontinence: Statistical Analysis Plan

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I. BACKGROUND and RATIONALE

Stress urinary incontinence (SUI) is the complaint of involuntary loss of urine on effort or physical exertion, or on sneezing or coughing(1). In a recent epidemiological study of pelvic floor disorders in US women, 25% reported the presence of at least one pelvic floor disorder (urinary incontinence, prolapse, and fecal incontinence), of which 17% reported symptomatic urinary incontinence(2). As SUI is the most common of female pelvic disorders, it was estimated in a cost analysis that $1.3 billion is spent on treatment of urinary incontinence annually, with SUI accounting for 82% of that cost(3). SUI can be managed by non-operative and operative therapy. Traditionally, first line therapy has consisted of non-operative interventions, which include behavioral therapy with pelvic floor muscle training or the use of a continence pessary. These interventions are less invasive and can be cost effective to the patient when compared to surgical intervention.

Continence pessaries are inexpensive, reusable vaginal inserts made of flexible silicone that are typically fit by a trained clinician in the office and managed by either the patient or the clinician. They come in various sizes and shapes to conform to a patient's vaginal cavity and provide structural support to the urethra. In a multi-centered randomized controlled trial of non-surgical management of SUI, 40% of participants in the continence pessary group reported "much better" or "very much better" SUI symptoms at 3 months, with 46% having greater than a 75% reduction in weekly urinary incontinence episodes (4).

In 2014, the FDA approved an over-the-counter disposable intravaginal device as another nonsurgical treatment for SUI. This device, the Poise Impressa®, is made of a non-absorbable nylon mesh that covers a core with 4 support poles made of resin and is housed in an applicator, similar to that of a tampon applicator(5). It is currently marketed as an over the counter non-surgical treatment of SUI, providing an effective alternative to physical therapy or surgery(6). Ziv et al conducted the initial study on this device, examining it over a 28 day period (comprised of a 14 day trial run followed by a 14 day observation period)(5). The authors found that 85% of participants experienced a $\geq$ 70% reduction in pad weight when using the device over the 14 day observation period. They also found that Poise Impressa® use was associated with an improvement in quality of life and had high patient satisfaction (5, 7).

The differences in these two devices are important and may result in major differences in patient satisfaction, compliance, and cost of use. The Poise Impressa® can only be worn up to 12 hours per day and is single use only, whereas the continence pessary can be worn continuously and is both reusable and reimbursable by insurance. To date, there has not been a comparative effectiveness trial performed to address this gap in knowledge. We aim to conduct a randomized comparative effectiveness trial of the continence pessary and the Poise Impressa® in order to provide patients and providers knowledge of the best nonsurgical treatment for women with SUI. We hypothesize that a physician fit continence pessary will provide greater subjective improvement in SUI symptoms, greater improvement in quality of life, greater patient satisfaction, and be lower cost as compared to the Poise Impressa®**.**

II. SPECIFIC AIMS

Specific Aim 1: To compare SUI symptom improvement between a continence pessary and the Poise Impressa® device. Improvement will be assessed using the Patient Global Impression of Improvement (PGI-I), a validated questionnaire assessing symptom changes(8).

Specific Aim 2: To compare quality of life, patient satisfaction, ease of device use, likelihood of continued use, and rates of adverse events between the continence pessary versus the Poise Impressa®. We will use validated questionnaires to assess participants' quality of life (9, 10). We will monitor for adverse events that are related or possibly related to the study device such as pain, vaginal bleeding, infections, and lacerations. We will use a Likert scale to assess patient satisfaction, ease of device use, comfort, and likelihood of continued use.

Specific Aim 3: To evaluate cost of use associated with each device. We will use cost of clinic visits and the cost of the device(s) to calculate estimated costs associated with device utilization**.**

III. METHODS

Experimental Design

This is a multi-centered randomized controlled trial of women with stress urinary incontinence or stress predominant mixed urinary incontinence who desire non-surgical therapy.

Study Population

Inclusion criteria:

- Female

- Age ≥ 21 years old based on Poise Impressa® manufacturing recommendations
- Pure stress urinary incontinence or stress predominant mixed urinary incontinence as determined by the Medical, Epidemiologic, and Social Aspects of Aging (MESA) Questionnaire (11). The MESA is a 16-item validated questionnaire intended to be utilized as a diagnostic questionnaire to evaluate SUI and urge urinary incontinence (UUI). 9 questions assess SUI and 7 assess UUI. Patients with scores in both categories are compared and the category with the highest score is identified as the predominant type of urinary incontinence.
- English-speaking

Exclusion criteria:

- Pregnancy. If patient is of childbearing potential and not using contraception a urine pregnancy test will be completed.
- Current urinary tract infection (UTI). Prior to enrollment all patients will have a urine dipstick performed. The presence of small/1+ or greater leukocytes and/or positive nitrites will require a urine culture to rule out infection. If the urine culture is positive (defined as >100,000 CFUs), the participant must be treated. After completing antibiotic therapy the participant will have repeat urine dipstick performed and if negative then the participant can proceed with baseline data collection. If repeat urine dip is positive (per same criteria as above) or the patient is symptomatic for a UTI, a repeat urine culture will be obtained in 2 weeks and the same steps followed before participant can be included in the study.
- Current vaginal infection based upon symptoms and/or clinician findings. Participants may be treated for vaginal infection and then proceed with baseline data collection once treatment is completed and they are symptom free.
- Currently taking overactive bladder medications. Participants may choose to discontinue overactive bladder medication. Upon successful completion of a 3-week washout period, they may proceed with baseline data collection.
- Received intradetrusor onabotulinum toxin A within the past 12 months.
- Underwent peripheral tibial nerve stimulation for OAB in the past 12 months.
- Previous sacral nerve stimulation implantation (InterStim) for current OAB treatment.
- Prior stress urinary incontinence surgery (i.e. midurethral sling or burch urethropexy)
- Postmenopausal bleeding of unknown etiology
- Neurogenic bladder
- Urinary retention (PVR>150 mL obtained via bladder scan or catheterization)
- Pelvic organ prolapse past the hymen as assessed by POP-Q examination (point Ba, C, D, or Bp > 0cm)
- Inability to complete questionnaires in English or comply with study protocol
- Inability to insert/remove an intravaginal device independently
- Significant symptomatic vaginal atrophy based on clinician findings. Patient may be treated and then re-evaluated for inclusion.
- Prior treatment or experience with either continence pessary or Poise Impressa®.

Interventions

Continence pessary

Participants will be fit for a continence pessary at a fitting appointment by their clinician as per their office protocol. Only continence rings or continence dish pessary will be used. Participants will be instructed on how to remove and reinsert the device so that they can use it at their discretion. Participants will be allowed to use the device during the menses if they desire. They will however be instructed to take the device out during sexual activity. Participants will return to the office at 2 weeks, +/- 4 days for a follow-up visit for assessment and refitting if needed per routine clinical practice. If they feel that the continence pessary needs to be refit, the participants will be asked to call for an earlier follow-up appointment per routine clinical practice.

Poise Impressa®

Participants will be given a sizing kit in the office and asked to select the size that they feel is appropriate per manufacturer's instructions. Once they have selected a size, they will be given a 2-week supply of their size. They will be asked to follow directions on use per the packet insert to simulate "real world use." The packet insert does reflect when the device is not to be used. This includes participants not using this during sexual activity or during their menses. Participants will return to the office at 2 weeks, +/- 4 days for a research visit to assess fit and if needed, change to a different size. At this visit they will be given the remainder of their device supply to complete the study. If they feel that they need a different size, the participants will be asked to contact the research staff for an earlier follow-up visit. Participants may use this device for up to 12 hours in a 24-hour period per the manufacturer's recommendation. As we are assessing efficacy in the setting of typical use, participants will be asked to use this device as they normally would if they were to purchase this on their own for the management of SUI.

Outcome Measures

Baseline demographics and characteristics will be extracted from the patient's electronic medical record including age, past medical, surgical, obstetric and gynecologic history, menopausal status, and hormonal therapy. The presence or absence of pelvic organ prolapse will be assessed via a pelvic organ prolapse quantification (POP-Q) examination that has to have been performed within one year of enrollment. Participants will be observed for 4 weeks and will complete validated questionnaires and a 3-day bladder diary to assess response to treatment.

Primary outcome: Success in SUI treatment defined as a response of "very much better" or "much better" on the Patient Global Impression of Improvement (PGI-I) (8). The PGI-I is a validated questionnaire assessing a patient's global improvement in symptoms following a specific intervention. Patients will be asked "Check the answer that best describes how your stress urinary incontinence is now, compared with how it was before you began using the continence device in this study." It is based on a 7-item Likert scale including "very much better," "much better," "a little better," "no change," "a little worse," "much worse," and "very much worse."

Secondary outcomes:
Quality of life (QoL): Participants' QoL will be assessed with the following three validated questionnaires:

1. Urogenital Distress Inventory (UDI-6)(9, 12): This short form 6-item questionnaire measures urinary incontinence symptom bother.
2. Urinary Incontinence Impact Questionnaire (IIQ-7)(9, 12): This short form 7-item questionnaire measures the functional impact of urinary incontinence.
3. Female Sexual Function Index (FSFI)(13): This 19-item questionnaire is used to assess sexual functioning in women.

These questionnaires will be completed by participants at baseline and then again at the end of the 4-week study period. A change score will be calculated by subtracting the two scores.

Interval Study Questionnaire: Participants will complete this questionnaire at weeks 2 and 4. It consists of questions addressing menstrual status, device use, adverse events, and Likert scale questions assessing *device satisfaction, ease of use, comfort, and likelihood of continued use.* The questions will consist of the following:

- "Did you have your period during the last 2 weeks?"
    - If yes, "During the last two weeks, how many days were you on your period?" and "During the last two weeks, how many days did you wear your device?"
- "On average, how many hours a day did you wear your device?"
- "How satisfied were you with the device?" Participants may respond with "completely satisfied," "somewhat satisfied," or "not at all satisfied," "(14).
- "In general, how comfortable is the device?" Responses include "completely comfortable," "somewhat comfortable," "not at all comfortable."
- Ease of use will be assessed by asking "how easy/difficult was the device to use?", "how easy/difficulty was the device to insert?" and "how easy/difficult was the device to remove?" Responses will include "very easy," "easy," "somewhat easy," "somewhat difficulty," "difficult," "very difficult."
- Likelihood of continued use will be assessed using the same Likert scale ranging from "strongly disagree" to "strongly agree" and asking participants to rate their level of agreement with the statement "I would continue to use this device in the future."
- Participants will also be asked, "If you had a friend or family member with stress urinary leakage, would you recommend this device to them?" Responses included "definitely would recommend," "probably would recommend," neutral or unsure," "probably would not recommend," "definitely would not recommend."
- Participants will also be asked if they have experienced any of the following: vaginal discomfort/pain, vaginal bleeding, vaginal infection, vaginal abrasion or laceration (cut in the vaginal tissues), urinary tract infection (bladder infection), other (with space to write in a response)

Additionally, participants will receive a phone call at 6 months during which general information regarding current device use and satisfaction will be collected via the follow-up questionnaire below. The PGI-I will also be administered verbally during these follow-up calls.

Follow-Up Questionnaire: Participants will complete this questionnaire at 6 months with a follow up phone calls and asked to respond to the following questions:

- "Are you still using the device provided to you during the study?"
    - If "yes", they will be asked "How satisfied are you with your current treatment?" Responses include "completely satisfied", "somewhat satisfied", or "not at all satisfied"
    - If "no", they will be asked several questions including:
        - Why are you not using the device? (select all responses that apply): "the device was too difficult to use", "the device did not work", " "the device was too expensive", "I am using a different treatment," "I am not bothered by my leakage" or "Other".

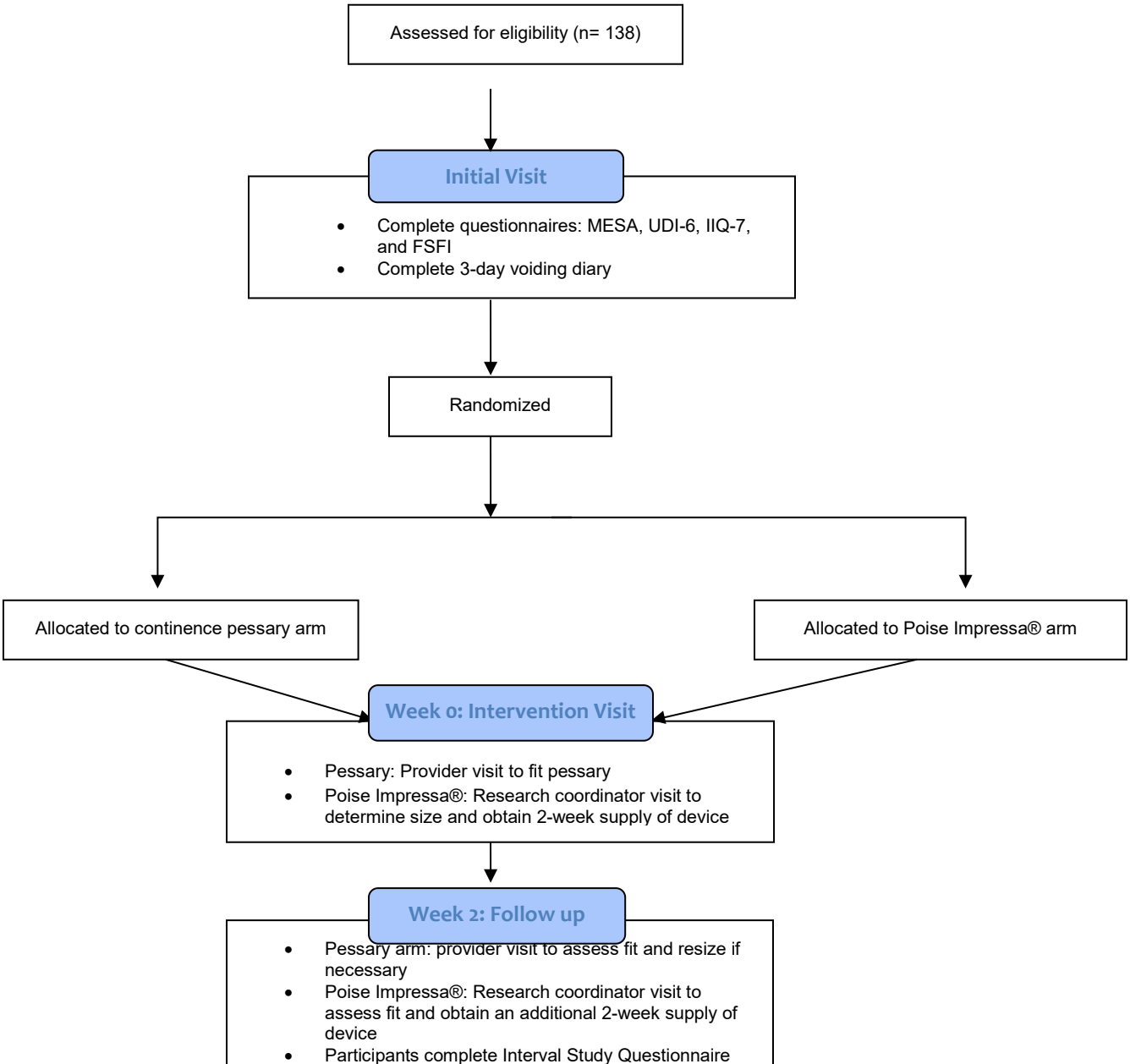
- Are you using another treatment? If yes, "what treatment are you using?" with options of pessary, impressa, physical therapy, surgery, other
- They will also be asked the PGI-I

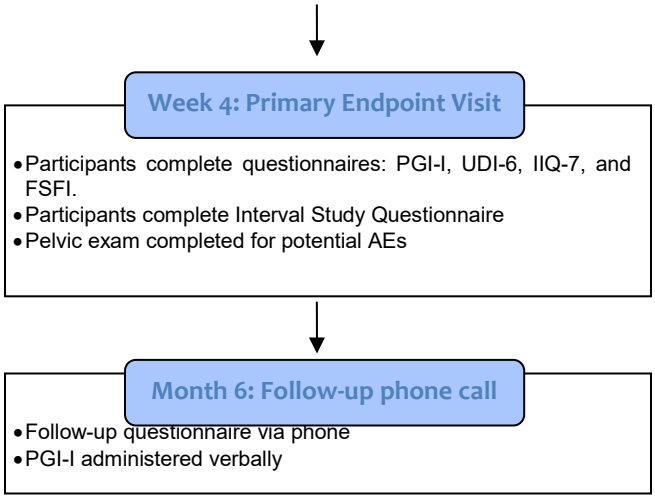
Adverse events (AEs): Potential AEs of interest include vaginal pain attributed to device use, vaginal bleeding, vaginal infection, vaginal abrasion/laceration, and urinary tract infection. Participants will be instructed to call and report any/all adverse events to research personnel and clinical staff. All AEs will be reported to the IRB of the institution at which the AE occurred (if required by site reporting guidelines), recorded in the research database, and if needed the patient will be scheduled for a clinical assessment. AEs will be assessed at each clinical/research visit and reported with study outcomes.

Cost analysis: For the Poise Impressa® device, cost calculations will include cost of sizing kit and devices, as well as costs associated with any refits. For the continence pessary, cost calculations will include the cost of the device, initial fitting visit and any additional clinic visits. Cost will be extrapolated to estimate annual cost of use for each device.

Study Visits
The study will consist of a four-week active observation period. Subsequently, there will be a follow up period consisting of a phone call at 6 months. (Figure 1: Study Flow Chart).

Figure 1. Study Flow Chart





Baseline Visit
Patients who are interested in the study will be consented and screened for inclusion/exclusion criteria. If there is concern for a urinary tract infection or vaginal infection, as previously defined in the exclusion criteria, further baseline data collection will be deferred until evaluation and treatment has been completed.

Participants will complete a demographics questionnaire and their medical and surgical history will be abstracted from electronic medical records. POP-Qs completed within the last year may be used to confirm study criteria; otherwise a new POP-Q must be completed. Participants will complete the MESA, UDI-6, IIQ-7, and FSFI questionnaires, and will then be randomized to an intervention group. Participants will be scheduled for their week 0 fitting visit, and then sent home with instructions to complete a 3-day bladder diary.

Fitting Visit (Week 0)
As described above participants will either undergo a pessary fitting or receive the Poise Impressa® fitting kit to determine proper sizing and the Poise Impressa® group will be given a two-week supply of the appropriately sized devices.

Week 2 Visit
All participants will complete the Interval Study Questionnaire and report on adverse events. All patients randomized to the continence pessary will undergo a pelvic exam per routine clinical practice to be assessed for possible refitting. Occurrence of any adverse events will also be assessed at that time. Participants randomized to the Poise Impressa® device will meet with research staff to assess size and if needed undergo resizing and will receive an additional 2-week supply of appropriately sized devices. For those participants in the Poise Impressa®, only those reporting symptoms concerning for adverse events will undergo pelvic exam by a clinical provider, otherwise an exam will be deferred in this group.

Week 4 Visit/End of Study
Participants will be asked to complete a 3-day bladder diary during the week preceding their week 4 visit. At their week 4 visit, participants will complete the PGI-I, UDI-6, IIQ-7, and FSFI questionnaires, as well as the Interval Study Questionnaire. All participants will undergo a pelvic exam to assess for any potential adverse events, such as vaginal abrasions, lacerations, or infections. This will complete the active portion of study participation.

Table 1: Study Assessments by Visit

Evaluation	Baseline	Week 0	Week 2	Week 4
Consent	X			
Demographics	X			
Device Fitting		X	X	
MESA	X			
3-day bladder diary	X			X
UDI-6	X			X
IIQ-7	X			X
FSFI	X			X
Interval Study Questionnaire			X	X
PGI-I				X

At the end of the visit the participant will be given information about the device they were not randomized to use. Participants that were randomized to the continence pessary will be given information on the Poise Impressa® and information on where they can purchase these devices as this would be routine in an office practice. Participants that were randomized to the Poise Impressa® arm can have a pessary fitting scheduled with a provider as part of routine care.

Participants can choose to pursue other options, such as surgery or pelvic floor physical therapy after completion of the study or if they choose to drop out. Participants that desire potential surgery will be scheduled with a physician for further discussion of their options. This visit is outside of the study and will be considered to be a routine follow up visit.

Month 6 Phone Call
The research assistant will call each participant 6 months after their week 0 visit (+/- 30 days) for a follow-up. During this call, participants will verbally complete the follow-up questionnaire as well as the PGI-I.

Participant Cost
There will be no out of pocket costs to the participant to participate in this study. The initial visit to the office is billed to the insurance company as this is a visit that is scheduled by the participant for a visit to address one or more of their pelvic floor disorders. Participants interested in non-surgical management of SUI are identified and offered enrollment if they meet all necessary criteria. Patients would receive a continence pessary as part of routine care if they were not enrolled in the study. Participants that are randomized to the continence pessary arm will have their insurance charged as part of standard of care for the device, intervention visit, week 2 visit, and any unscheduled visits. As week 4 is considered a study visit, they will not be charged for this visit. Participants that are randomized to the Poise Impressa® arm will have their devices provided free of cost, along with their study visits (intervention visit, week 2, and week 4) since it is not standard of care to provide these devices or have follow up visit as patients are able to purchase these over-the-counter without physician guidance. Any unscheduled visits due to an adverse event will be considered a billable visit since a patient would come to the office for this problem if they were using this device outside of the study.

Participant Incentive
All participants will receive $10 upon study completion.

Statistical Analysis
Randomization
Participants will be randomized to either continence pessary or Poise Impressa® in a 1:1 ratio through random permutated blocks of 4 and 6 stratified by institution. Randomization will be conducted via REDCap to ensure proper randomization and to aid in allocation concealment.

Sample Size Estimate
We aim to detect a clinically significant difference of 50% improvement with continence pessary versus 25% with the Poise Impressa®. Assuming an 80% power, an alpha error of 5% and a 20% dropout rate we need 138 participants total (69 per group) to detect this difference. We plan to assess for differences in secondary outcomes between arms while acknowledging that we may be underpowered to detect significant differences in these outcomes.

Statistical Analysis
De-identified data from the study database will be analyzed. Continuous variables will be analyzed by students t-test and categorical variables will be analyzed by chi-square or Fischer's exact tests. A regression analysis will be performed for both continuous and discrete outcomes in order to simultaneously adjust for baseline demographics and characteristics in addition to treatment effects. A p-value of less than 0.05 will define statistical significance and 95% confidence intervals will be documented. Our primary outcome, SUI treatment success as assessed by PGI-I score, will be analyzed by an intention-to-treat. A per-protocol analysis will also be performed as a planned secondary assessment of the primary outcome. All statistical analysis will be performed using SPSS. Data will be presented according to CONSORT 2010 guidelines for randomized controlled trials(15).

<u>Null hypotheses</u>
The null hypothesis for each outcome will be that there is no difference in the primary outcome between the continence pessary and Poise Impressa® groups.

Baseline Characteristics

Baseline characteristics will be assessed using descriptive univariate analyses to characterize the total study population. Histograms will be generated to characterize the distribution of the specific outcome being assessed. The baseline characteristics of the two study arms will be analyzed using the Student's t test for continuous variables, and Chi-Square or Fisher's exact tests for categorical variables. Although a comparison of the baseline characteristics between study arms is not necessarily needed given the randomized design, this is a study of 150 people and so we have planned to include a regression analysis.

Equivalence Testing

Our purpose is to compare the two treatment methods in regards to the primary outcome not to assess equivalence of these two therapies. We have calculated a sample size based on a clinically significant difference in the primary outcome such that if there is no a significant difference detected then we can conclude that a clinically significant change is not present.

Missing Data and Participant Dropout

We will make all efforts to ensure we have complete data on all patients in the study. Due to the randomized design we do not anticipate a significant difference in drop out rates between the two groups. However, if there is significant missing data or if there is a significant difference in drop out rates between arms we will consult a biostatistician to discuss how best to account for this difference.

Expertise and Collaborations

Dr. Alexis Dieter will be responsible for database maintenance and for creating the initial statistical computations. Dr. Jennifer Wu will be responsible for overseeing the statistical computations. Dr. Dieter and Dr. Wu are both experienced researchers who have previously designed, performed and completed data analysis for RCTs and who have each completed formal training in statistical analysis and methodology for clinical research. If any concerns arise, we will obtain a biostatistics consultation to ensure all data is properly analyzed.

Feasibility

We aim to recruit up to 138 participants in a 12-month period. In order to be able to complete participant enrollment and observation within one year of study initiation, we will be collaborating with the Division of Urogynecology at the University of North Carolina. In 2015 the division performed approximately 50-100 continence pessary fittings for SUI. Both sites have already obtained independent funding for their study costs.

Adverse Events and Potential Pitfalls

We will monitor for adverse events (AEs), such as bleeding or ulceration from device use, throughout the study and all AEs will be reported to the IRB of the institution at which the AE occurred if required by site reporting guidelines. Potential pitfalls include failure to recruit sufficient participants. If needed we will extend the enrollment period and will consider providing additional financial incentives for participation.

Data Storage

All study data will be recorded on case report forms by study staff. All paper and electronic data will be securely maintained in locked research offices at each site. It will be stored within the offices of the Division of Female Pelvic Medicine and Reconstructive Surgery at the Ohio State University Wexner Medical Center and within the offices of the Division of Urogynecology at the University of North Carolina at Chapel Hill, accessible only to study personnel. Data will be entered into an electronic database by study staff and that database will be stored on a password-protected server.

IRB Approval and Clinical Trials Registration

IRB approval will be obtained through each institution individually with each site to ensure IRB approval remains current and updated for their site. Dr. Silpa Nekkanti of the Division of Urogynecology at Ohio State University Wexner Medical Center will be responsible for registering and maintaining the study on clinicaltrials.gov.

IV. SIGNIFICANCE

This novel randomized trial will provide valid and valuable information to help inform patients and clinicians regarding the most effective nonsurgical treatments for SUI. The results of this study will also advance women's health as SUI is a highly prevalent condition and the ability to pursue nonsurgical options may decrease the morbidity associated with SUI surgeries.

V. STUDY TIMELINE

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14
IRB approval														
Recruitment														

Data Collection														
Data analysis														
Preparation of results														
Study Closeout														

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