Early Feasibility Prospective Open-Label Study to Assess the Function of a Novel Pessary for the Non-Surgical Management of Pelvic Organ Prolapse

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REVISION HISTORY

Version #	Version Date	Summary of Changes	Approver
1	2/17/2020	Submission to D-HH IRB for reliance letter	PH
2	5/26/2020	Include 2.25 and 2.5 in. diameter pessaries	PH
3	9/13/2020	Include 3 in. diameter pessaries (retracted)	PH
4	11/5/2020	Include ring pessaries users in inclusion criteria, include 3 inch diameter study pessaries, number of subject increased to 15-20	PH

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1.0 Study Summary

Table of Study Summary:

Study Title	Early Feasibility Prospective Open-Label Study to Assess the Function of a Novel Pessary for the Non-Surgical Management of Pelvic Organ Prolapse
Study Design	Early feasibility study of a medical device
Primary Objective	• To assess the ability of the study device to be retained during Valsalva compared to the ability of the subject's current pessary to be retained during Valsalva (by measuring the distance from each pessary's leading edge to the hymen) • To assess the ability of the study device to be retained throughout regular activity (by vaginal examination)
Secondary Objective(s)	• To assess the shape of the study pessary during expulsion if it is not able to be retained (by vaginal examination) • To assess the orientation of the study pessary stem following regular activity (by vaginal examination) • To assess the discomfort experienced with removal of the subject's current pessary compared to the discomfort experienced with removal of the study pessary (by visual analog scale) • To assess the discomfort experienced with insertion of the subject's current pessary compared to the discomfort experienced with insertion of the study pessary (by visual analog scale) • To globally assess the comfort associated with use of the study pessary (by verbal description)
Research Intervention(s)/ Investigational Agent(s)	Temporary placement and assessment of a novel vaginal pessary
IND/IDE #	Device to be considered for an abbreviated IDE (non-significant risk device)
Study Population	Current users of a ring style or Gellhorn pessary for treatment with Stage II or greater pelvic organ prolapse
Sample Size	15-20
Study Duration for individual participants	One hour
Study Specific Abbreviations/ Definitions	HRT – Hormone Replacement Therapy POP – Pelvic Organ Prolapse POP-Q – Pelvic Organ Prolapse Quantification UI – Urinary Incontinence VAS – Visual Analogue Scale FPMRS – Female Pelvic Medicine and Reconstructive Surgery

2.0 Objectives

This is an early feasibility, open-label, non-randomized trial to obtain preliminary information about the function and effectiveness of a novel vaginal pessary for the use in women who suffer from symptoms of pelvic organ prolapse (POP). Recruited subjects will have Stage II POP or greater and will be current users of a legally marketed vaginal pessary. In a single visit, data will be collected on the performance and comfort of the subject's current pessary. After fitting and placement of a study pessary, comparative data will be collected between subject's current pessary and the study pessary on ability to support prolapse. The study pessary's function will be assessed under controlled circumstances. The subject will have her current pessary replaced at the conclusion of the visit. Results will be used to inform future design modifications of the study pessary.

3.0 Background

POP is a prevalent condition that can be observed in over 50% of women over the age of 50.[1] POP results from a weakening of the pelvic floor connective tissue and muscles, allowing the uterus or vaginal walls to descend. Typical symptoms, which include bulge and pressure, urinary dysfunction, defecatory dysfunction, and sexual dysfunction, can result in physical discomfort, emotional distress, and disrupt activities of daily life. Using published data on weighted prevalence rates of specific pelvic floor disorders[2] in conjunction with US census data, it can be estimated that the number of US women with symptomatic prolapse in 2016 was 3.6 million. The lifetime risk for a woman to have surgery for pelvic organ prolapse is 12.6%, or 1:8.[3] As the specialty of Female Pelvic Medicine and Reconstructive Surgery (FPMRS) matures and surgical outcomes are being followed with more scrutiny, it is becoming increasingly clear that surgical treatment options are less effective than once believed. The 3 most effective and commonly performed procedures for apical prolapse have estimated composite recurrence rates by 6 years of 43%, 49%, and 57%.[4]

The vaginal pessary is an effective treatment option which is inserted in the vagina and acts as a shelf resting upon the pelvic floor muscles to support the descending organs. Often, it is as effective to abate the burdens of prolapse as a successful reconstructive surgery. 77% of practicing urogynecologists recommend a vaginal pessary as the first line treatment option for their patients with POP.[5] Based on this number, statistics cited above, and financial information from current pessary makers, there are ~2.3 million women in the United States who use a pessary for POP. A pessary is not surgically implanted and can be removed and reinserted but is only effective while in situ. The root cause failure of current pessaries in common use is their rigid and fixed design, which makes them difficult or impossible for patients to remove and insert independently. Consequently, medical practitioners in the United States see most pessary users 3-4 times per year to temporarily remove the pessary, clean it, examine the vagina for epithelial erosions, and then reinsert the pessary.[6] These steps are needed to avoid preventable complications associated with long term pessary use which have been reported as high as 56%[7] and include vaginal erosion, bleeding, increased discharge, as well as discomfort

and dysfunction in voiding and defecation.[8] Furthermore, women who experience less severe forms of prolapse and who do not need the support of their pessary outside of strenuous physical activity often must wear their pessary when not necessary, which induces additional lifestyle impacts such as impairing a woman's ability to engage in sexual intercourse.

The two most commonly used pessary types on the market are the ring style and the Gellhorn pessary. The Gellhorn pessary is clinically more effective to reduce the life impact of prolapse symptoms,[9] and once fit has longer continuation rates than the ring with support (10.5 years vs. 1.8 years).[10] Additionally, the Gellhorn successfully treated 71% of women at 3 months who failed treatment with the ring with support.[11] Yet most practitioners, particularly Ob/Gyn physicians who are not additionally specialized in FPMRS, preferentially prescribe the ring with support because it is easier and more intuitive to use. The Reia Vaginal Pessary (study pessary) has been engineered to overcome the liabilities related to difficulty for physicians and patients to remove and re-insert the pessary. The Reia Vaginal Pessary has a structural form similar to the Gellhorn and is hypothesized to be simpler and more intuitive to use than the ring with support.

4.0 Study Endpoints

The primary and secondary endpoints of the study are described in the following table:

Type	Name	Time Frame	Brief Description
Primary	To assess the ability of the study device to be retained during Valsalva compared to the ability of the subject's current pessary to be retained during Valsalva (by measuring the distance from each pessary's leading edge to the hymen)	During treatment	The subject will be asked to Valsalva with their current pessary in place, and the distance from the leading edge of the current pessary to the hymen will be measured in centimeters. After the current pessary is removed and the patient is fit with an appropriate study pessary, the subject will be asked to Valsalva again. The distance from the leading edge of the study pessary to the hymen will be measured in centimeters. In order to assess the ability of the study pessary to function and be retained, the measurements will be compared.
Primary	To assess the ability of the study device to be retained throughout regular activity (by vaginal examination)	During treatment	With the study pessary in place, the subject will be asked to ambulate for 10 minutes and attempt to void. Following these activities, whether the pessary was retained or expelled will be recorded.
Secondary	To assess the shape of the study pessary during expulsion if it is not able to be retained (by vaginal examination)	During treatment	The subject will be asked to Valsalva. If the study device is expelled during Valsalva, whether the study device was expelled fully deployed or whether it prematurely folded to its collapsed state will be recorded.

Secondary	To assess the orientation of the study pessary stem following regular activity (by vaginal examination)	During treatment	Following ambulation and attempting to void and prior to removing the study pessary, it will be recorded if the study device's stem rotated out of its original inserted position.
Secondary	To assess the discomfort experienced with removal of the subject's current pessary compared to the discomfort experienced with removal of the study pessary (by visual analog scale)	During treatment	To indicate discomfort, the subject will be shown and asked to mark a visual analogue scale (VAS) after removal of her current pessary and before using the study pessary. The VAS will be a 10 centimeter linear continuum in which 0 represents no pain and 10 represents worst pain. After use of the study pessary and upon removal of the study pessary, the subject will be shown and asked to mark another VAS. In order to assess the discomfort experienced during removal of the study pessary, the distance from 0 to the subject's mark will be measured and compared between the two scales.
Secondary	To assess the discomfort experienced with insertion of the subject's current pessary compared to the discomfort experienced with insertion of the study pessary (by VAS)	During treatment	To indicate discomfort, the subject will be shown and asked to mark a VAS after insertion of the study pessary. The VAS will be a 10 centimeter linear continuum in which 0 represents no pain and 10 represents worst pain. After use of the study pessary and upon insertion of the subject's current pessary, the subject will also be shown and asked to mark another VAS. In order to assess the discomfort experienced during insertion of the study pessary, the distance from 0 to the subject's mark will be measured and compared between the two scales.
Secondary	To globally assess the comfort associated with use of the study pessary (by verbal description)	Post treatment	Following insertion of the subject's current pessary, and after the subject is dressed, she will be asked whether the study pessary was more, less, or as comfortable as her current pessary when it was in situ. If she responds it was more or less comfortable, she will be asked to describe why.

Safety endpoints cannot be reasonably assessed in this study because risks to subjects are minimal given the short duration of the study intervention (anticipated to be approximately 30 minutes) and the nature of the planned intervention. Pain will be measured as described in the secondary endpoints above. Unanticipated events will be tracked and followed per established FDA guidelines for monitoring investigations of medical devices (21 CFR §812.46).

5.0 Study Intervention/Investigational Agent

Please see attached document for device description and non-significant risk rationale.

6.0 Procedures Involved

Methods

Current users of existing marketed pessaries typically present to their providers every 3-4 months so that their pessary can be removed and cleaned and their vagina can be inspected for erosion caused by their device. Fifteen subjects will be recruited for this study from a panel of established patients who present for this routine care of their ring style or Gellhorn pessary to a clinical practice at the Dartmouth-Hitchcock Clinic specializing in Female Pelvic Medicine and Reconstructive Surgery (FPMRS). Inclusion will be based on pre-defined criteria outlined in "10.0 Inclusion and Exclusion Criteria." There will not be discrimination based on race or ethnicity. It is anticipated that most participants will be post-menopausal as this reflects the demographic of women who suffer from this disorder. Treatment intervention will be non-blinded to the subject and investigator and will occur in a single visit. Each subject will receive the study pessary and wear it in a controlled environment for less than 1 hour. Assessment of the study pessary's performance to support the subject's prolapse will be determined by measuring the baseline distance between the leading edge of each subject's current pessary to the hymen and comparing that to the measured distance between the leading edge of the study pessary to the hymen, as well as by observing the ability of the study pessary to be retained with simulated activities of daily life such as walking and toileting. Secondary outcomes of subject comfort with insertion, use, and removal of the study pessary will be measured.

The study pessary is the only device which will be used in this trial, though the subject will arrive for her visit and leave with her current pessary. There will be no placebo devices placed. The study pessary is not cleared by the FDA, and a rationale is provided for a non-significant risk device claim in the attached documents. This trial was devised so that it could take place at the time in which subjects present for usual care of their current pessary, and the procedures are consistent with the standard of care at Dartmouth-Hitchcock Medical Center, the site of the study.

Study Procedures

- Exam – Subject will be asked to disrobe and will be positioned in the lithotomy position per routine. Visual inspection of the vulva will be conducted to note for atrophy and determine the absence of open wound or tear near the opening of the vagina or perineum *[would be done anyway]*.
- Position of the current pessary will be determined in relation to hymen - subject will be asked to Valsalva, and the position of the leading edge of the current pessary in relation to the hymen will be recorded in centimeters *[research purposes]*.
- The current pessary will be removed and the vagina will be inspected for erosion. Current pessary size and stem length will be recorded *[would be done anyway]*. Pain with removal will be recorded by VAS, a 10 centimeter linear continuum in which 0 represents no pain and 10 represents worst pain. Pelvic floor muscle strength will be subjectively recorded by the examiner by instructing the subject to "Kegel" with

examining fingers in the vagina *[research purposes]*. The current pessary will be washed with anti-bacterial soap and tap water *[would be done anyway]*.

- The study pessary that maps to the size of the subject's current pessary should be selected at random from the inventory of study pessaries will be removed from its sealed bag and the study pessary's serial number (labeled on the bag) will be recorded. The study pessary will be lubricated and placed, and the position of the pessary in relation to the hymen will be recorded (in centimeters, with Valsalva). Pain with insertion will be recorded by a VAS administered with pessary insertion and removal. If the study pessary is expelled with Valsalva, this will be recorded, and a notation will be made if it was expelled in its deployed state or secondary to it prematurely collapsing. In the event a 2.25 inch study pessary is expelled, the subject will be refit with a 2.5 inch study pessary and the steps in this section will be repeated. Likewise, if a 2.5 inch study pessary is first selected and it is expelled, the subject will be refit with a 3 inch study pessary and the steps in this section repeated. *[research purposes]*.
- The subject will dress, ambulate, and void - the subject will be asked to get dressed, walk for 10 minutes, void, and return to the office then disrobe again. If the study pessary is expelled during this activity, this will be recorded *[research purposes]*.
- The study pessary will be removed. The orientation of the study pessary inside the vagina will be noted prior to removal. Discomfort with removal will be recorded by VAS. The study pessary will be washed with anti-bacterial soap and tap water and inserted into a resealable bag along with its original packaging. The used study pessary should be returned to Dr. Hanissian's office which is adjacent to the clinic space where the study is being conducted *[research purposes]*.
- The current pessary will be re-inserted, *[would be done anyway]* and pain will be recorded by VAS *[research purposes]*. The subject will give a global impression of study pessary comfort in comparison to current pessary *[research purposes]*.

Data Collected

After the subject provides consent, the subject's medical record will be abstracted for their medical history. The subject may be asked to clarify the medical record. Data to be collected includes:

<u>Medical History</u>

- Age
- BMI (kg/m^2)
  - <20
  - 20-30
  - >30
- Previous gynecologic surgeries
  - Hysterectomy
  - Prior prolapse surgery
  - Prior UI surgery

  - Other gynecologic surgery

- Previous non-surgical prolapse treatment
  - Pelvic floor exercises
  - Pessary use
- Parity
  - No. of births
  - No. of vaginal births
- Estrogen status
  - Pre-menopausal
  - Post-menopausal
  - HRT
- Concomitant disorders
  - Urinary Incontinence
  - Fecal Incontinence
  - Other
- Prolapse stage
- POP-Q measurements prior to pessary fitting

Outcomes

- Pessary retention and function
  - Retained, normal position
  - Comes out fully deployed before ambulation
  - Collapses and comes out before ambulation
  - Comes out during ambulation
  - Comes out when on toilet, attempting void
- Rotation during ambulation
- Distance from the leading edge of the pessary to hymen with Valsalva
  - Original pessary
  - Study pessary
- Discomfort with insertion and removal (VAS completed by subject)
  - Original pessary
  - Study pessary
- Difficulty with insertion and removal (5 point scale completed by provider)
  - Original pessary
  - Study pessary
- Global impression of comfort while using pessary (3 point scale completed by subject)
- Global impression of ease of use (5 point scale completed by provider)

See attached data collection forms. Forms will be filled out in ink and stored according to procedures outlined in "17.0 Data Management and Confidentiality."

Transition from Research Participation

At the conclusion of the study, each subject will have her current pessary replaced in her vagina, and she will be instructed to present for her next routinely scheduled follow up visit per her typical care.

7.0 Data and Specimen Banking

N/A

8.0 Sharing of Results with Subjects

The performance of the study pessary will be verbally shared with each subject who is interested at the time of the visit.

9.0 Study Timelines

It is anticipated that each participant will be involved in the study for approximately one hour. The study is designed to enroll 15 subjects presenting for routine pessary care to the Division of Female Pelvic Medicine and Reconstructive Pelvic Surgery at Dartmouth-Hitchcock Medical Center. This study site sees an average of 50 patients per month for routine pessary care of which 80% are using a ring style or Gellhorn pessary and would be eligible to participate. Assuming 1:8 patients who is eligible agrees to participate, it should take 3 months to recruit patients and complete this study.

10.0 Inclusion and Exclusion Criteria

Sex of Subjects

Pelvic organ prolapse (POP) is a disease which only affects females, most typically those who are post-menopausal. Males will not be recruited for this study.

Age of Subjects

Study participants will be at least 18 years old. Pelvic organ prolapse is primarily a disease of post-menopausal women and is therefore not relevant to the population of women less than 18 years old.

Racial and Ethnic Origin

Pelvic organ prolapse (POP) is a disease which only affects females, most typically those who are post-menopausal. Males will not be recruited for this study. This is an early feasibility study in which 15 subjects will be recruited from a clinical practice at Dartmouth-Hitchcock Medical Center, a tertiary care facility in Lebanon, NH. Eligible subjects will be screened for participation sequentially as they present for routine pessary care without excluding individuals based on race or ethnicity. 2018 US Census estimates for nearby Claremont, NH, which has similar demographics to Lebanon, demonstrates a population which is 97.6% White alone, 0.9% Black or African American alone, and

0.4% Asian alone. 2.4% are Hispanic or Latino. The population recruited for this study would have similar characteristics.

Inclusion Criteria

- Women with Stage II pelvic organ prolapse or greater
- Current ring style or Gellhorn pessary users inclusive of sizes 1.5"-3.5"
- Capable of giving informed consent

Exclusion Criteria

- Pregnancy
- Deep vaginal erosion noted with removal of current pessary
- Presence of vesicovaginal fistula
- Presence of rectovaginal fistula
- Vaginal, rectal, or bladder tumor
- Inflammatory Bowel Disease
- Presence of open wound or tear near vagina or anus by exam prior to removal of current pessary
- Current vaginal or urinary infection requiring treatment
- Previous pelvic floor surgery in last 12 months
- Congenital malformation of bladder, rectum, or vagina
- Significant medical condition interfering with study participation (psychologic, neurologic, active drug/alcohol abuse, etc.)
- Planning pregnancy in next 6 months

Vulnerable Subjects

Subjects will not be recruited to this study if they are identified as a member of a vulnerable population.

11.0 Vulnerable Populations

N/A

12.0 Local Number of Subjects

15 subjects will be recruited for this study. Typical early feasibility studies for medical devices include 5-15 subjects. The upper bound was selected due to the variability of the presentation of prolapse (apical, anterior, or posterior, as well as degree of severity) to evaluate performance of the Reia Vaginal Pessary across a broader range of clinical presentations.

13.0 Recruitment Methods

Method of Subject Identification and Recruitment

Subjects will be recruited from a panel of established patients in a clinical practice specializing in FPMRS at the Dartmouth-Hitchcock Clinic. There will be no advertisements. Screening for potential subjects during a given week of care will be

based on scheduled visit type, duration, and type of pessary currently in use. Prospective subjects will have their name, medical record number, and telephone number recorded on a handwritten list with pen and paper. With the list complied, subjects will be contacted by telephone, and using the submitted phone script (see attached document), their interest in participation will be gauged. The list will be shredded after all potential subjects are contacted. If they demonstrate a preliminary interest, they will be scheduled for the appropriate amount of time to complete consent in-person and enter the study as they present for their pessary care visit. Additionally, the recruiter will offer to mail prospective subjects a copy of the consent form to review ahead of their appointment. Preferred mailing addresses will be collected over the telephone and handwritten directly on the mailing envelope and not copied elsewhere.

Payment for Participation

Participants will be offered a $100 gift card in compensation for the time due to participation that is in excess of the typical time required for routine pessary care.

Alternatives to Participation

If the patient elects not to participate in the study, they will proceed with their usual appointment and care.

14.0 Withdrawal of Subjects

Reasons for a subject to be withdrawn from the research study include:

- The subject is found to have a condition which does not allow participation in the research, such as a finding upon physical examination that excludes them from the study.
- The subject has a reaction that requires immediate removal of the research pessary.

If a subject is removed, already collected data may not be removed from the study database and will be handled with the same protocol as research data. The subject will receive the usual ongoing care for their pessary.

15.0 Risks to Subjects

This study will involve greater than minimal risk. The subject could experience minor discomfort with insertion and deployment of the study pessary, while she is being asked to Valsalva, or if the study pessary is expelled with Valsalva. There could be minor abrasion of the vaginal epithelium with the study pessary upon insertion or removal or disruption of the perineal epithelium. The risk of these events occurring should be lower than them occurring during usual care because the study pessary collapses to a smaller diameter than current devices. The study pessary could become dislodged during ambulation or voiding, which may cause embarrassment.

16.0 Potential Benefits to Subjects

Subjects will not directly benefit from participation in this study.

17.0 Data Management and Confidentiality

Each subject who has signed a consent form and entered the study will be assigned a random study 3 digit number (001-999). Data related to the study will be handwritten on data collection forms (see attached document). The case report forms will not contain unique identifiers and will be referenced back to subjects only using the assigned study numbers. A separate key will be created linking the subjects with their random numbers. Once the key is created, it will remain in a locked cabinet which contains other study related documents (including, but not limited to, the protocol, instructions for use, all versions of the consent form, etc.). These documents will be maintained by study personnel through the trial and for 2 years after termination of the study and will only be accessible by study personnel.

Unidentifiable data from the case report forms may be collated in spread sheets for purposes of analysis. Such data will be exclusively stored and processed exclusively on password protected and encrypted computers.

Confidentiality protections include Dartmouth-Hitchcock Clinics confidentiality training for all employees and annual refresher seminars for all employees. Despite these protections, investigators will discuss with the eligible participants the potential for inadvertent disclosure of their data and ensure they are fully aware of these minimal, but possible risks. Breaches in confidentiality will be reported to Western IRB.

Reia, LLC is partially funded by the NIH. Reia is subject to potential auditing at any time by the NIH or the FDA. Reia, LLC may be required to release data from this study to these agencies if an audit were to be performed and this information were to be requested. The sponsor, monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to subjects' medical records to conduct and oversee the research. Excluding this circumstance, Reia, LLC will not intentionally release information to any individual, agency, or entity.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Data Analysis and Data Monitoring

This is a non-randomized, non-blinded, early feasibility study involving a vaginal pessary. Given that this intervention is known to be safe and well-tolerated, there are 15 subjects with only one visit per subject, and the total time to recruit all subjects is anticipated to be 3 months, we do not believe a formal data safety monitoring committee is required. However, a data and safety monitoring plan will be in place. The data safety monitoring plan will focus on low intensity monitoring by the Data Safety Monitoring Team, comprised of the participating clinicians. The Data Safety Monitoring Team will meet every other week, or sooner if necessary, to review subject accrual, adherence to

study protocol, and ensure prompt reporting of serious and adverse events to Western IRB and the study sponsor (Reia, LLC).

At each contact with the subject, the clinical investigator will seek information on adverse events by specific questioning and by examination. Information on all adverse events will be recorded for review by the Data Safety Monitoring Team. Moderate adverse events will be reviewed by the Data Safety Monitoring Team within one week. Serious adverse events, as defined by FDA criteria, will be reviewed by the Data Safety Monitoring Team within 24 hours and reported to Western IRB and the study sponsor (Reia, LLC). Careful monitoring of the recruitment, enrollment, study procedures, and adverse events will help protect the safety of the subjects and quality of the data.

Any unanticipated adverse device effects will be immediately evaluated by the sponsor, Reia, LLC. If it is determined that the adverse device effect presents an unreasonable risk to the subjects, the investigation will be terminated within 5 working days of making the determination and not more than 15 working days of first receiving notice.

In compliance with 21 CFR §812.46, if the sponsor, Reia, LLC, discovers that the study team is not complying with the signed agreement, the study protocol, applicable FDA regulations, or any conditions for approval of this IRB application, then Reia, LLC will either secure compliance or stop delivery of the device and terminate the investigator's participation. Additionally, Reia, LLC will require the remaining investigational devices be returned.

Protection Against Risks

Most risks for participating in this study are associated with discomfort in use of the study pessary, either with insertion, removal, or unintentional expulsion. Per the above protocol, the subject will be awake and unsedated for the complete encounter and will be able to communicate any discomfort experienced, and the subject's level of discomfort will be assessed at several points.

It is unlikely that an incidental finding will be discovered since the study population presents for similar care every 4 months. In the event there is a finding, the member of the clinical research team who has been providing treatment for the subject will follow through to provide appropriate care or make appropriate referrals.

Adverse events will be classified as Grade 1 or mild (easily tolerated by the subject no intervention necessary), Grade 2 or moderate (causing discomfort or interrupting usual activities), or Grade 3 or severe (causing considerable interference with usual activities, may be incapacitating, or may require hospitalization). Treatment of any adverse event, if indicated, will be coordinated by the member of the clinical study team who provides typical care for the study participant. Specific adverse events will be monitored as outlined in the data and safety monitoring plan described in the above section.

Additionally, the clinical research team will report any adverse events (regardless of whether the event is serious or non-serious) which are *unexpected* and *related to the research procedures* within 5 working days to the study sponsor (Reia, LLC) and Western IRB. Grade 4 (life threating consequences requiring immediate intervention) and Grade 5 (death related to adverse event) terminate the study and will be reported to Western IRB and the study sponsor within 24 hours.

The subject will have the opportunity to stop the study at any point if desired. She will never leave the facility while using the study pessary and will, therefore, have immediate access to care if a problem arises. The subject will be given a copy of the consent form which lists the telephone numbers for the triage nurse of the principle investigator, as well as a 24-hour telephone number for the on-call physician if concerns arise after study participation.

No publication or public presentation about the research described above will reveal the subject's identity. Once data collected for this research study is no longer identifiable, the data may be used for other purposes. Protected health information will be handled as described in "13.0 Recruitment Methods" and "17.0 Data Management and Confidentiality."

19.0 Provisions to Protect the Privacy Interests of Subjects

All subjects recruited for this study will have previously received outpatient care for management of their pessary in the FPMRS division at the Dartmouth-Hitchcock Clinic. Upon arrival for a study visit, the patient will be checked in for care in the standard manner, forming a single line 10 feet back from the reception desk. They will then be brought to either a patient exam room or a private consultation room to meet with a member of the study team who will guide them through the consent process. Once this has been completed, they will be given a chance to void, then brought to an exam room by an LNA or RN and be joined by a member of the study team. Given the sensitive nature of conditions treated in the Ob/Gyn department, all care is delivered in areas not accessible to the public. The bathrooms and exam rooms are private. The study team is comprised of clinicians who are sub-specialty trained in FPMRS and facile at asking the questions and performing the procedures outlined in the study protocol.

20.0 Compensation for Research-Related Injury

As included in the attached consent form, if the subject develops an illness or sustains an injury due to the research study, the study sponsor (Reia, LLC) will pay for the reasonable costs of medical treatment. The sponsor will not pay for:

- Treatment of illness or injury that results from the negligence of a health care provider, or
- Treatment of a condition the subject had before they were in the study.

The sponsor will not offer any other payments for study-related illness or injury such as lost wages, expenses other than medical care, or pain and suffering.

21.0 Economic Burden to Subjects

Participation in this study should not lead to additional cost for the subjects. Laboratory testing will not be performed, nor are there reasonably anticipated events which will require additional care or follow up. Since participation will happen at the time of routine care, there will not be additional travel expenses incurred.

22.0 Consent Process

Process of Consent

Each subject who presents for a study visit will be shown to a private room by a member of the clinical research unit or a member of the clinical study team. The purpose of the study will be reviewed, and if the subject continues to be interested in participation, then study eligibility will be confirmed, and the informed consent process will begin. Each subject will be given a copy of the consent form. Based on their preference, the form will be read to them aloud or they can read it independently. Each section will then be summarized; questions will be encouraged and answered fully. The subject will then be asked to teach back the information presented in that section to ensure comprehension before moving on to the next section.

The consent document will then be signed and dated by the subject providing consent and the person obtaining consent. A copy of the consent document will be scanned into the subject's medical record and a copy will be given to the subject. The original will be kept in the locked cabinet with other research documents.

As part of the process, subjects will be given as much time as they need to decide on participation. If they appear to be feeling pressure or need more time, they will not be enrolled in the study. If at any point the subject indicates she does not want to take part in the research, the informed consent process will be stopped.

Subject Capacity

Potential subjects for recruitment to this study are known to the FPMRS clinical team and their baseline capacity is known. The subject will not be entered into the study if there is concern regarding capacity to provide consent based on a change in function from previous encounters, or any of the following:

- A diagnosis of dementia or cognitive impairment.
- History of an evaluation of dementia since the last encounter in the FPMRS clinic.
- A report, in medical records or from a family member or person well acquainted with the subject, that the subject has symptoms of cognitive impairment or dementia.

- An abnormal degree of confusion, forgetfulness, or difficulties in communication that is observed in the course of interacting with the subject.
- Psychotic symptoms, bizarre or abnormal behavior exhibited by the subject.

Subject Comprehension

As described above, after the subject has read or been read the consent document, each section will again be verbally reviewed and summarized. In this step, comprehension will be determined by a "teach back" method.

23.0 Process to Document Consent in Writing

Consistent with the standard operating procedure: *Written Documentation of Consent (HRP-091) of the D-HH Human Research Protection Program* (local IRB), the informed consent process will begin when the subject agrees to take part in the study and end when the consent process is documented in writing. The consent form (see attached) has been written in understandable language and has signature blocks for the printed name, signature and date for both the subject and the person obtaining consent (the principle investigator, co-investigator, research assistant, or coordinator). The subject will receive either a photo copied version or a second signed version of the consent form.

24.0 Setting

The study will take place at Dartmouth-Hitchcock Medical Center in the Faulkner Ambulatory Building, Level 5, in the Department of Obstetrics and Gynecology. Subjects will be cared for in exam rooms typically used for delivering clinical care of patients in the FPMRS division.

25.0 Resources Available

Fifteen subjects will participate in this study, and participation will be limited to one visit on the day of enrollment. The identified study site sees an average of 50 patients per month for routine pessary care of which 80% are using a ring style or Gellhorn pessary and would be eligible to participate. Assuming 1:8 patients who is eligible agrees to participate, it should take 3 months to recruit patients and complete this study.

The Dartmouth-Hitchcock Clinic encompasses Dartmouth-Hitchcock Medical Center, a 381-bed hospital and the primary teaching hospital associated with the Geisel School of Medicine at Dartmouth. Outpatient care for patients seen in the Division of Female Pelvic Medicine and Reconstructive Surgery is provided on the 5th floor of the adjoining Faulkner Ambulatory Building. The clinic is a shared space with the Department of Obstetrics and Gynecology with a dedicated entrance, registration, and scheduling desk. Within the shared departmental clinical space, there are 30 exam rooms and 3 consult rooms in addition to two shared workrooms for provider documentation. Annually, there are over 2000 new patients seen at Dartmouth-Hitchcock with the diagnosis of pelvic organ prolapse (POP), and approximately 250 visits for new pessary fittings. The Dartmouth-Hitchcock Clinic utilizes an EPIC electronic medical record charting system

and has an electronic data warehouse which is searchable by diagnosis, procedures, and visit type.

The members of the study team are a cohesive group of practitioners who work together at The Dartmouth-Hitchcock Clinic providing clinical care. The study team will include five practitioners who have patients regularly scheduled for care in the study site and who will be available to provide medical treatment, should subjects develop an illness or injury because of their participation in the research study.

The investigator team and sponsor will meet as a group to review the consent form, protocol, instructions for use, data collection form, and phone script prior to commencing the study. Each member of the team will have adequate time to review the documentation and the opportunity to ask questions to the sponsor and principal investigator. During this meeting, the principal investigator will also assign duties and functions to each member of the team.

26.0 Multi-Site Research

N/A

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