Protocol

Study Title: Assessment of effectiveness and safety of a novel pessary for the non-surgical management of pelvic organ prolapse

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| **Protocol Number:** | CP-002-01 |
| **Sponsor:** | Reia, LLC ("Reia")<br>331 River Road<br>Lyme, NH 03768 |
| **Medical Monitor:** | Paul Hanissian, MD<br>331 River Road<br>Lyme, NH 03768 |
| **Principal Investigator:** | Kris Strohbehn, MD |
| **Study Site for Principle Investigator:** | Department of Obstetrics and Gynecology<br>Dartmouth-Hitchcock Medical Center<br>One Medical Center Drive<br>Lebanon, NH 03756<br>Kris.Strohbehn@Hitchcock.org<br>Direct phone number for office of the PI: 603 653-9312<br>24-hour phone number: 603 650-5000 |

## REVISION HISTORY

| Revision | Revision Date | Summary of Changes/Affected Sections |
|---|---|---|
| 01 | 3-16-2021 | Initial release of document, submission to IRB |
| 02 | 8-25-2021 | Updated to include recommendations from site initiation visits |
| 03 | 5-17-2022 | Updated to allow Visit 2 to be a phone call & recruitment strategies |

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## 1.0 Study Summary

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| **Study Title** | Assessment of effectiveness and safety of a novel pessary for the non-surgical management of pelvic organ prolapse |
| **Study Design** | Prospective open label feasibility study of a medical device |
| **Primary Objective** | • To assess the effectiveness of the study pessary to support prolapse by measuring the change in the score of the Pelvic Floor Distress Inventory-20 (PFDI-20)<br>• To assess the safety of the study pessary |
| **Additional Objective(s)** | • To assess proportion of subjects who are successfully fit and can retain the study pessary<br>• To assess the subjects' ability to insert and remove the study pessary<br>• To compare subjects' discomfort experienced with insertion and removal of their current pessaries with study pessaries<br>• To globally assess satisfaction associated with use of the study pessary |
| **Research Intervention(s)/ Investigational Agent(s)** | Replacement of a subject's current pessary with a study pessary for use over a three-month time interval |
| **IND/IDE #** | Device to be considered for an abbreviated IDE (non-significant risk device) |
| **Study Population** | Current users of a Gellhorn or ring style pessary for management of Stage II or greater pelvic organ prolapse |
| **Sample Size** | 40, excluding withdrawals |
| **Study Duration for individual participants** | 4 months |
| **Study Specific Abbreviations/ Definitions** | CRAIQ – Colorectal Anal Impact Questionnaire<br>EMR – Electronic Medical Record<br>FPMRS – Female Pelvic Medicine and Reconstructive Surgery<br>FSF – Female Sexual Function<br>IIQ – Incontinence Impact Questionnaire<br>IUGA – International Urogynecological Association<br>PFDI-20 – Pelvic Floor Distress Inventory-20<br>PFIQ-7 – Pelvic Floor Impact Questionnaire-7<br>PFMT – Pelvic Floor Muscle Training<br>PISQ-IR – Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, IUGA-Revised<br>POP – Pelvic Organ Prolapse<br>POP-Q – Pelvic Organ Prolapse Quantification<br>POPIQ – Pelvic Organ Prolapse Impact Questionnaire<br>UI – Urinary Incontinence<br>VAS – Visual Analogue Scale |

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| | WCG IRB – Western Copernicus Group IRB |

## 2.0 Objectives

The purpose of this study is to obtain preliminary data on the effectiveness, safety, function, comfort, and patient satisfaction with a novel vaginal pessary design for the use in women who suffer from symptoms of pelvic organ prolapse (POP) and have already opted for non-surgical management. Recruited subjects will have Stage II POP or greater and will be current users of a Gellhorn or ring style pessary. Following enrollment, each subject will enter a 1-month wash out period in which they will continue using their current pessary so that baseline subjective and objective data can be collected. They will then be fit with a study pessary and enter a 3-month treatment phase. Comparative, subjective and objective data will be collected at the conclusion of the study.

## 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 for POP. A pessary is inserted in the vagina and acts as a shelf resting upon the pelvic floor muscles to support the descending organs. A pessary is not surgically implanted and can be removed and reinserted but is only effective while in situ. Often, pessaries are as effective as reconstructive surgery in improving the symptoms of prolapse. 77% of practicing urogynecologists recommend a vaginal pessary as the first line treatment option for their patients with POP.[5] It is estimated that there are ~2.3 million women in the United States who use a pessary for POP, based on financial information from pessary makers and the above epidemiologic data on POP. 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 at least 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 pessaries on the market are the "ring with support" 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 style pessaries because they are easier and more intuitive to use. The Reia Vaginal Pessary (study pessary) has been engineered to improve the comfort and ability of pessary removal and reinsertion by physicians and patients. The Reia Vaginal Pessary has a structural form similar to the Gellhorn, but is collapsible, and is hypothesized to be simpler and more comfortable to use than ring style pessaries. This hypothesis is preliminarily supported by data obtained in an early feasibility, in-office trial with 15 subjects (NCT04275089).

## 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 | Pelvic Floor Distress Inventory-20 (PFDI-20) | Between enrollment and the end of washout period (before treatment) [Week 0-4] and post treatment [Week 16] | The Pelvic Floor Distress Inventory - 20 (PFDI-20) is a validated instrument to assess the presence and bother of symptoms that pelvic floor disorders have on health-related quality of life in women. It is a 20-item questionnaire and the short form of the 46 question PFDI. There are three subscales: Urinary Distress Inventory 6 (UDI-6), Colorectal-Anal Distress Inventory 8 (CRADI-8), and the Pelvic Organ Prolapse Distress Inventory 6 (POPDI-6). The overall score range is 0-300. The higher the score, the greater the perceived impact that pelvic floor dysfunction has on a patient's life. The minimal important change in the |

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| | | | PFDI-20 to demonstrate a clinical effect in women choosing conservative management of their prolapse (i.e. a pessary) is between 13.5 and 18.3 points. |
| Primary | Prevalence and severity of adverse events that subjects experience using the study pessary compared to those experienced with their current pessary | Throughout study [Week 0-16] Adverse events can occur with use of the current pessary or during the treatment phase with the study pessary. They can be experienced with insertion or removal of either the current or study pessary, noted on physical exam, or reported at any time. | Adverse events experienced with insertion or removal of the current or study pessary include: pelvic cramping or discomfort, perineal tear, failure of the study pessary to deploy or collapse, or pessary expulsion. Adverse events noted on physical exam include: vaginal irritation, vaginal ecchymosis, vaginal abrasions/superficial cuts, vaginal erosion, vaginal bleeding, vaginal discharge, or urinary retention. Adverse events which could occur at any time include: pelvic cramping or mild discomfort, copious vaginal discharge, urinary tract infection, substantial discomfort, pessary expulsion (collapsed or deployed), or adverse events unrelated to the pessary or study visit. Each event will be classified as mild (transient and easily tolerated by the subject), moderate (causing discomfort or interrupting usual activities), or severe (causing considerable interference with usual activities, may be incapacitating, or may require hospitalization). |
| Secondary | Pelvic Floor Impact Questionnaire (PFIQ-7) | Between enrollment and the end of washout period (before treatment) [Week 0-4] and post treatment [Week 16] | Pelvic Floor Impact Questionnaire -7 is a health-related quality of life instrument, designed to assess the life impact of pelvic floor symptoms in women with pelvic floor disorders. The PFIQ-7 has a parallel structure to the PFDI with 3 Scales: CRAIQ, POPIQ and IIQ. |
| Secondary | Pelvic Organ Prolapse/Urinary Incontinence Sexual | Between enrollment and the end of washout period (before treatment) | A validated evaluation tool which can be used clinically as well as in research for assessment of female |

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| | Questionnaire, IUGA-Revised (PISQ-IR) | [Week 0-4] and post treatment [Week 16] | sexual function (FSF) in women with female pelvic floor disorders. |
| Secondary | Objective assessment of the pessary's ability to support the prolapse | At enrollment [Week 0], during treatment [Week 3-5], and during treatment [Week 16] | POP-Q points Ba and Bp (measurements of prolapse) will be measured during physical exam, with the pessary in situ. |
| Secondary | Global assessment of study pessary satisfaction compared to current pessary | For current pessary at the end of washout period [Week 3-5]; For study pessary post treatment [Week 16] | Satisfaction will be assessed using a Visual Analog Scale (VAS) with a 10 cm linear continuum in which 0 represents no satisfaction and 10 represents complete satisfaction. |
| Secondary | Pain associated with study pessary insertion compared to current pessary | During treatment [Week 3-5], during treatment [Week 5-7], and post treatment [Week 16] | Pain will be assessed using a Visual Analog Scale (VAS) with a 10cm linear continuum in which 0 represents no pain and 10 represents worst pain. |
| Secondary | Pain associated with study pessary removal compared to current pessary | During treatment [Week 3-5], during treatment [Week 5-7], and post treatment [Week 16] | Pain will be assessed using a Visual Analog Scale (VAS) with a 10cm linear continuum in which 0 represents no pain and 10 represents worst pain. |
| Other | Proportion of subjects successfully fit with the study pessary | Post treatment [Week 16] | Proportion of subjects who were successfully fit with the study pessary. |
| Other | Change in frequency of pessary removal for self-managers | Post treatment [Week 16] | The monthly frequency of pessary self-removal during the washout period will be compared against monthly frequency of self-removal in the treatment phase. |
| Other | Ease of insertion of study pessary by subject for self-managers | Post treatment [Week 16] | Ease will be assessed using a Visual Analog Scale (VAS) with a 10cm linear continuum in which 0 represents most difficulty and 10 represents most ease. |
| Other | Ease of removal of study pessary by subject for self-managers | Post treatment [Week 16] | Ease will be assessed using a Visual Analog Scale (VAS) with a 10cm linear continuum in which 0 represents most difficulty and 10 represents most ease. |

## 5.0 Study Intervention/Investigational Agent

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

## 6.0 Procedures Involved

### Methods

This is a non-randomized prospective trial. Treatment intervention will be non-blinded to the subject and the investigator. Subjects will serve as their own controls and enter the treatment phase of the study after a 1-month washout period of using their current pessary. Subjects will be recruited for this study from panels of patients in clinical practices 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."

The primary outcome measure will be the change in the scores of the Pelvic Floor Distress Inventory-20 (PFDI-20), administered first during the washout period while still using their current pessary and then at the conclusion of the treatment phase with the study pessary. The PFDI-20 is a validated health-related quality of life instrument to assess the *presence and bother of symptoms* in women with pelvic floor dysfunction. For women with relatively mild pelvic floor symptoms, a minimal important change (MIC) of between 13.5 and 18.3 points in the PFDI-20 score can be considered clinically relevant. At least fifty subjects will be enrolled, expecting that after drop-out and attrition at least 40 subjects will have completed the study. This provides power of .80 for a MIC equivalence limit of 17 points on the PFDI-20 scale.

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.

The study will take place over 4 visits (Visit 0, Visit 1, Visit 2, and Visit 3).

Visit 0 *[research purposes]* will involve screening, enrollment, consent, subject questionnaires, and chart abstraction for historical data and will take place during a regularly scheduled pessary maintenance visit. The current pessary size and type will be recorded, and it will be observed in situ for the presence of rotation and its ability to support prolapse by measuring the distance of the most dependent compartment of the subject's prolapse to the hymen (POP-Q points Ba and Bp), as well as the distance from the leading edge of the current pessary, if a Gellhorn, to the hymen. After removal of the current pessary, a baseline physical exam will be conducted to assess for pre-existing vaginal pathology (ecchymoses, abrasions, superficial cuts, erosions, granulation tissue, bleeding) or urinary retention associated with current pessary use. Other exam elements will include assessment of vulvovaginal atrophy, pelvic muscle strength, perineal descent, and POP-Q points GH (with strain) and TVL. After cleaning, the current pessary will be replaced, and each subject will begin the washout period where they continue use of their current pessary. Either at this first visit or during the washout period, each subject will complete the PFDI-20, PFIQ-7, and PISQ-R to establish baseline scores. Self-

managers will track the frequency of removals. If the current pessary cannot be reinserted, they will be treated according to standard of care.

Visit 1 *[research purposes]* will aim to be scheduled between 3 and 5 weeks from Visit 0 (the conclusion of the washout period). Demographic and historical data will be extracted from the Electronic Medical Record (EMR) if not completed at Visit 0 and supplemented by the subject as needed. Global subject satisfaction of the current pessary will be assessed using a Visual Analog Scale (VAS) with a 10 cm linear continuum in which 0 represents no satisfaction and 10 represents complete satisfaction. As in Visit 0, the current pessary will be observed in situ for the presence of rotation and its ability to support prolapse by measuring the distance of the most dependent compartment of the subject's prolapse to the hymen (points Ba and Bp), as well as the distance from the leading edge of the current pessary to the hymen. The current pessary will be removed, washed, placed in a sealed bag, labeled and either stored or given to the subject for them to return with at their final visit. The physical exam will be repeated as in Visit 0, and the presence of perineal disruption associated current pessary removal will be noted. The appropriate study pessary size for the subject based on the provided mapping from the subject's current pessary and practitioner's expertise will be selected at random from the inventory of study pessaries, removed from its sealed bag, and the study pessary's serial number (labeled on the bag) will be recorded. The subject will be fit with the study pessary. If a study pessary cannot be fit, and the patient is willing, they can be fit with a different sized pessary at Visit 1 or can remain in the study and return for a second attempt to be fit with a study pessary at Visit 2. A VAS will be used to assess the perceived discomfort with removal of the current pessary and, separately, with insertion of the study pessary. For self-managers, ease of current pessary removal and reinsertion will be noted using a VAS and teaching will be provided on the proper technique to insert and remove the study pessary.

Visit 2 *[research purposes]* has the option to be omitted, at the discretion of the practitioner and the subject, and will be aimed to be scheduled within 1-3 weeks of Visit 1. The subject will receive a phone call just prior to this visit. The subject will be asked about pessary use and adverse events. If the subject is doing well without any study related concerns, the practitioner and subject can decide if this visit can be omitted. The purpose of this visit is to minimize unforeseeable risks associated with use of the study pessary and/or to refit a subject with a study pessary if the original one was expelled or could not be inserted during Visit 1. If conducted in person, physical exam will be performed to assess for vaginal pathology (ecchymoses, abrasions, superficial cuts, erosions, granulation tissue or bleeding) or urinary retention related to the study pessary, and all adverse events will be recorded. The study pessary will be observed in situ for the presence of rotation and its ability to support prolapse by measuring the distance of the most dependent compartment of the subject's prolapse to the hymen, as well as the distance from the leading edge of the study pessary to the hymen. Those subjects who

were not successfully fit with a study pessary in their first visit would be fit with a new study pessary.

Visit 3 *[research purposes]* will occur at the conclusion of the 3-month (from Visit 1) treatment phase - a typical length of time between routine visits for patients who choose long term pessary management of their prolapse. It can be scheduled in a window between 11 and 13 weeks from Visit 1. When the subject returns for Visit 3, a physical exam will be repeated, as in previous visits, for comparative data. The study pessary will be observed in situ for the presence of rotation and its ability to support prolapse by measuring the distance of the most dependent compartment of the subject's prolapse to the hymen (Points Ba and Bp), as well as the distance from the leading edge of the study pessary to the hymen. A VAS will be used to assess discomfort with removal of the study pessary, discomfort with reinsertion of their current pessary, and their global satisfaction of the study pessary. The subject will have been instructed to return with their current pessary which was removed in Visit 1. If the subject's current pessary is not brought to the visit, they will be given a new pessary of the size and style of their current pessary. Each subject will complete the PFDI-20, PFIQ-7, and PISQ-R for a post treatment comparison. For self-managers, other data collected will include frequency of removal and a VAS for ease of study pessary insertion and removal.

Additional Visits: Subjects will be seen as necessary and adverse events will be managed according to standard of care. If the study pessary falls out after Visit 1, the subject may be seen at their convenience for reinsertion or resizing. If a study pessary cannot be fit and retained, the subject will be withdrawn from the study and their current pessary will be placed. If the subject's current pessary is not brought to the visit, they will be given a new pessary of the size and style of their current pessary.

Special Circumstances: If a subject dies between Visit 1 and Visit 3, an attempt will be made to contact the coroner to retrieve the study pessary. If the study pessary cannot be retrieved, a copy of the death certificate will be obtained.

The study pessary is the only device that will be used in this trial. 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.

## Data Collected

See attached data collection forms. The data collected will be obtained through chart abstraction, verbal history, questionnaire responses, visual analogue scale response, and physical exam.

Data collected on adverse events will be described in "18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects."

Forms will be filled out electronically or 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 their current pessary replaced in their vagina, and they will be instructed to present for their next routinely scheduled follow up visit per their typical care. If a subject lost their original pessary or if they do not bring it to the final visit, they will be supplied with a new pessary identical to their original at no additional cost.

## 7.0 Data and Specimen Banking

N/A

## 8.0 Sharing of Results with Subjects

Composite study results will be shared with the subjects upon request following publication.

## 9.0 Study Timelines

Participation for each enrolled subject will last 4 months as outlined in the table below.

| **Visit #** | **Week** | **Purpose** | **Summary of Key Tasks/Measures** *(see "6.0 Procedures Involved" for additional details)* |
|---|---|---|---|
| 0 | 0 | Recruitment, physical exam, beginning of washout period | Consent;<br>Assessment of prolapse support with current pessary, assessment of adverse events with current pessary |
| 1 | 3-5 weeks from Visit 0 | Data collection, physical exam, removal of current pessary, fitting of study pessary | PFDI-20, PFIQ, and PISQ-R;<br>VAS for discomfort with insertion and removal of pessaries;<br>Re-assessment of prolapse support with current pessary, re-assessment of adverse events with current pessary |
| 2 | 1-3 weeks from Visit 1 | Assessment of adverse events, refitting of study pessary if necessary | Physical exam (if in person) and history |

| | | | |
|---|---|---|---|
| 3 | 11-13 weeks from Visit 1 | Completion of trial, data collection, physical exam, removal of study pessary, reinsertion of current pessary | PFDI-20, PFIQ and PISQ-IR;<br>VAS for discomfort with insertion and removal of pessaries;<br>Assessment of prolapse support with study pessary, assessment of adverse events with study pessary |

## 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 subjects will be at least 18 years old. Pelvic organ prolapse is condition primarily developed post-menopause and is therefore not relevant to the female population under 18 years old.

### Racial and Ethnic Origin

This is a safety and efficacy study in which at least 50 subjects will be recruited. Eligible subjects will be screened for participation sequentially as they present for routine pessary care at the study sites without excluding individuals based on race or ethnicity. The distribution of race and ethnicity for potential subjects will reflect the demographics of patients in the practices at the sites.

### Inclusion Criteria

- Females with Stage II pelvic organ prolapse or greater
- Users of a Gellhorn (inclusive of sizes 2”-3.25”) or ring style pessary (inclusive of sizes 2.5-3.5”) for >3 months’ duration
- Fluency in English or Spanish
- Capable of giving informed consent

### Exclusion Criteria

- Pregnancy
- Short vaginal length (total vaginal length < 8 cm), or subjective vaginal narrowing
- Deep vaginal erosion noted with removal of current pessary
- Presence of vesicovaginal fistula
- Presence of rectovaginal fistula
- Current treatment for vaginal, rectal, or bladder tumor
- Presence of open wound or tear near vagina or anus by exam prior to removal of current pessary

- Presence of pelvic, vaginal, or urinary infection requiring treatment
- Ongoing treatment of recurrent urinary tract or vaginal infections
- Inflammatory bowel disease
- Chronic pain syndromes of pelvic or anorectal origin
- 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

Total study recruitment across all sites will have a requirement to include a minimum of 12 subjects (approximately 25%) who currently use a Gellhorn pessary and a minimum of 12 subjects who currently use a ring style pessary to best characterize the current landscape where the Reia Pessary will be used. Current users of Gellhorn pessaries are more likely to have advanced baseline prolapse, and current users of ring style pessaries are more likely to be self-managers. It is important for both demographics to be represented in this study.

### Vulnerable Subjects

The following groups of subjects will not be recruited: pregnant females, prisoners, females in mental health facilities, employees of the study site, and students attending any of the study institutions.

## 11.0 Vulnerable Populations

N/A

## 12.0 Recruitment Methods

### Method of Subject Identification and Recruitment

Subjects will be recruited from panels of established patients in the clinical sites, and will occur in one of three ways:

1. Subjects can be informed about the study as they present for routine pessary care, and if interested, handed a consent form for review, then booked for Visit 0 at the time their next routinely scheduled pessary maintenance visit. Please see attached patient flyer document.
2. If a Partial HIPAA Waiver is granted, subjects can be recruited with a letter, flyer, and/or a screening telephone call ahead of a normally scheduled visit. Potential subjects will be identified during a given week of care based on scheduled visit type, duration, and type of pessary currently in use. Their name, medical record number, and telephone number recorded on a handwritten list with pen and paper. With the list complied, subjects may be contacted by mail, using the submitted

letter and/or flyer, and/or telephone, using the submitted phone script (see attached document), and 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 send electronically or mail prospective subjects a copy of the consent form to review ahead of their appointment. If the latter, preferred mailing addresses will be collected over the telephone and handwritten directly on the mailing envelope and not copied elsewhere.

3. Subjects can also be recruited for participation at the time of an already scheduled visit if there is latitude in the schedule to extend the visit and complete the consent process and other aspects of Visit 0.
4. Advertisements (pending IRB approval) will be posted on social media, online, and/or in print.

### Payment for Participation

Subjects will be offered three separate $100 gift cards in compensation for their time due to participation that is in excess of routine pessary care. Visits 0 and 3 would occur as part of routine care. A $100 gift card will be provided after completing Visits 1 and 2 (even if conducted as a phone call) for extra time and travel, as well as at Visit 3 upon completion of the study. In total, subjects will have received $300 at the completion of the study.

### Alternatives to Participation

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

## 13.0 Withdrawal of Subjects

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

- The subject is found to have a condition that does not allow participation in the research, such as a finding upon physical examination that excludes them from the study.
- The subject no longer tolerates their current pessary during the washout period or needs a different size or type of pessary during the washout period.
- The subject is not able to be fit with a study pessary at the conclusion of Visit 2, or the study pessary is repeatedly expelled.
- The study pessary causes discomfort or adverse reaction for which continued use is contraindicated.
- The subject has a reaction that requires immediate removal of the study pessary.
- The subject may withdraw themselves at any point for unforeseen circumstances.

If a subject is removed from the study, 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.

## 14.0 Risks to Subjects

This study will involve greater than minimal risk. The subject could experience:

- Discomfort during insertion, use, or removal of the study pessary.
- Minor abrasion of the vagina or perineum with insertion or removal of the study pessary.
- Vaginal bleeding caused by the study pessary.
- Increased vaginal discharge caused by the study pessary.
- Vaginal epithelial erosion (superficial or deep) from using the study pessary.
- Difficulty urinating or leakage of urine caused by the study pessary.
- Difficulty with defecation caused by the study pessary.
- Embarrassment if the study pessary falls out.
- Minor discomfort if the study pessary rotates out of position or if it falls out.
- Inconvenience caused by the inability of the study pessary to support the subject's prolapse.

Each of the risks cited above exist for any patient who chooses a pessary for management of their prolapse and are not unique to the study pessary. Though inconvenient, these are not life threatening.

The novelty of our pessary lies in its ability to flex, which we hypothesize will make insertion and removal more comfortable for the subject. Because it does not contain buttons, mechanism, or moving parts, it does not have mechanical features subject to failure. The soft and pliable nature of the molded silicone should not be capable of pinching the vaginal epithelium when the study pessary is elongated for removal, but this metric will be followed.

In common clinical practice, patients often use their pessaries continuously for 3-6 months without removal or medical evaluation. Per our protocol, the Reia pessary is intended to be used for 3 months continuously, and each subject will be evaluated 1-3 weeks after the study pessary is initially placed to assess for the presence of adverse events. Each subject will be a current pessary user, and during the course of the trial they will be monitored more closely than had they continued to use their existing pessary.

## 15.0 Potential Benefits to Subjects

Subjects will not directly benefit from participation in this study.

## 16.0 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 either be recorded on data collection forms (see attached document) or collected in REDCap. 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 be kept secure with 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 spreadsheets for purposes of analysis. Such data will be stored and processed exclusively on password protected and encrypted computers.

Confidentiality protections include 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 WCG 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, and 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 patient information to any individual, agency, or entity.

## 17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

### Data Analysis and Data Monitoring

This is a non-randomized, non-blinded, feasibility study involving a vaginal pessary. Given that the intervention is known to be safe and well-tolerated and the total exposure to our pessary for each subject was chosen to be similar to the typical interval of continuous pessary use which is common in clinical practice for current pessary users, we don’t 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 one clinician from each participating site and a biostatistician. The Data Safety Monitoring Team will meet monthly, or sooner if necessary. Their charge will be to review subject accrual,

adherence to study protocol, and monitor adverse events. Additionally, they will ensure prompt reporting of serious adverse events to WCG 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 which represent a change in baseline from those experienced in the washout period 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 WCG 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 that are possibly, probably, or definitely related to the study intervention 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

The primary somatic risks for participating in this study are associated with either discomfort or with pathologic changes to the vagina. Discomfort can occur with insertion, removal, unintentional expulsion or with daily use. Per convention, each subject will be awake and unsedated while the study pessary is being fit and will be able to communicate any discomfort experienced. A physical exam will be performed at each study visit. Pathologic changes to the vagina, which can be noted during these times, include vaginal ecchymoses, abrasions, superficial cuts, erosions, granulation tissue, or bleeding. Subject reported adverse events include pelvic cramping or mild discomfort, copious vaginal discharge, urinary tract infection, urinary retention, substantial discomfort, pessary expulsion (deployed or collapsed), pessary failure to deploy or collapse, or adverse events unrelated to the pessary or study visit.

Each adverse event 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 Grade 1, Grade 2, or Grade 3 adverse events that are *unexpected* and possibly, probably, or definitely *related to the research procedures* within 5 working days to the study sponsor (Reia, LLC) and WCG IRB. Grade 4 (life threating consequences requiring immediate intervention) and Grade 5 (death related to adverse event) that are unlikely, possibly, probably, or definitely related to the intervention will terminate the study. These adverse events will be reviewed by the Data Safety Monitoring Team within 24 hours and reported to WCG IRB and the study sponsor (Reia, LLC).

It is unlikely that an incidental finding will be discovered since the study population presents for similar care every 3-4 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.

The subject will have the opportunity to stop the study at any point if desired. The subject will be given a copy of the consent form which lists the telephone numbers for the nursing staff and lead investigator at each site, as well as a 24-hour telephone number for the on-call physician if concerns arise.

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.”

## 18.0 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 their study site. Upon arrival for a study visit, the subject will be checked in for care in the standard manner per existing clinical protocols designed to maintain privacy. 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 study visit. 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.

## 19.0 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.

## 20.0 Economic Burden to Subjects

Participation in this study should not lead to additional cost for the subjects beyond the time and travel associated with the two additional visits related to study participation (Visit 1 and Visit 2). Laboratory testing will not be performed nor are there reasonably anticipated events which will require additional care or follow up. As stated above, subjects will be given three separate $100 gift cards for study participation, one for each of the visits which occur in addition to routine care, and one at the conclusion of the study.

## 21.0 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, 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 they do 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.

## 22.0 Process to Document Consent in Writing

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 a photocopied version.

## 23.0 Multi-Site Research

There will be at least 50 participants recruited for this study across all sites. All subjects will be identified using the methods described in "12.0 Recruitment Methods," and recruited using the same phone script (submitted separately for review), with site specific information substituted as indicated.

The investigator teams across all sites 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. The sponsor will additionally visit each site to train the practitioners and set up the study materials in the designated locations. 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, and then sign a training log to document this process. During this meeting, the Principal Investigator will also assign

duties and functions to each member of the team. Monthly research video teleconferences will be held between the Sponsor, the Principal Investigator, and the study sites to review progress in executing the study, as well as to communicate successes and challenges. Additionally, the sponsor will communicate directly with each study site on an ad hoc basis to coordinate changes in the protocol, consent forms, other study related documents, or other information necessary for subject safety or study execution.

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