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A Prospective Randomized Efficacy Study Comparing a Pelvic Digital Health System Home Program of Pelvic Floor Muscle Exercise to Kegel Exercises in the Treatment of Stress-Predominant Urinary Incontinence

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Project No.: Renovia-05
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A Prospective Randomized Efficacy Study Comparing a Pelvic Digital Health System Home Program of Pelvic Floor Muscle Exercise to Kegel Exercises in the Treatment of Stress-Predominant Urinary Incontinence

FDA Statement

The *leva* Incontinence System is an investigational medical device under development. It has been designed to meet the requirements of IEC 60601-1:2005 (3RD Edition), Medical Electrical Equipment-Part 1: General requirements for basic safety and essential performance; IEC 60601-1-2:2014 (4th Edition), Medical electrical equipment-Part1-2:General requirements for basic safety and essential performance-Collateral standard: Electromagnetic compatibility-Requirements and tests; and IEC 60601-1-1-11, General requirements for basic safety and essential performance-Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment. In addition, all materials that will come into contact with the patient have undergone biocompatibility evaluation satisfying ISO 10993-1 requirements. All patient contacting materials have been tested, and passed cytotoxicity, sensitization and irritation or intra-cutaneous standards. *Leva* poses little to no risk to the patient if used as instructed.

The *PFDx* device is an investigational medical device currently used to gather data related to pelvic floor health. It uses substantially equivalent technology to the *leva* Incontinence System, an FDA-approved, Class II medical device. Whereas the *leva* device uses 6 accelerometer sensors, the *PFDx* device uses 12 sensors, allowing for a more complete evaluation of a woman's physiology. The *PFDx* device is shaped as a ring that sits in the fornix with a thin, flat strip that descends along and out of the vagina. At the end of the device (outside the woman's body) is a small enclosure that houses a microprocessor and a Bluetooth Low Energy radio. The *PFDx* communicates wirelessly to the associated Chromebook ClinApp in a similar manner to the *leva* device. All sensors related components are over-molded with the same biocompatible silicone material used to manufacture

the *leva* device. Given the similarity of *PFDx* and *leva*, along with independent risk analysis, *leva Plus* is considered a "non-significant risk device" as defined by 21 CFR 812.3(m).

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

This document is confidential. It contains proprietary information of Renovia, Inc. Any viewing or disclosure of such information that is not authorized in writing by Renovia, Inc. is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

1 PROTOCOL REVISION HISTORY

Date/Name	Description
23 March 2018	Version 1.0
28 March 2018	Version 1.1
6 April2018	Version 1.2
18 April 2018	Version 1.3
09 May 2018	Version 1.4

PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Prospective, Nested, Randomized Efficacy Study Comparing a Pelvic Digital Health System Home Program of Pelvic Floor Muscle Exercise to Kegel Exercises in the Treatment of Stress-Predominant Urinary Incontinence

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A Prospective, Nested, Randomized Efficacy Study Comparing a Pelvic Digital Health System Home Program of Pelvic Floor Muscle Exercise to Kegel Exercises in the Treatment of Stress-Predominant Urinary Incontinence

Signature

Date

2 TABLE OF CONTENTS

3 SYNOPSIS

Device:	*Leva* PLUS Pelvic Digital Health System
Clinical Indication:	Urinary Incontinence
Study Objective:	Primary objectives: • Compare the efficacy of using a novel intravaginal system (leva® Plus Pelvic Digital Health System™) to perform pelvic floor muscle exercises (PFME) compared to a Kegel exercise home program in women with stress-predominant urinary incontinence (SUI). HYPOTHESIS: The leva® Plus Pelvic Digital Health System is superior to a home PFME program in the treatment of stress-predominant urinary incontinence. HYPOTHESIS: The leva® Plus Pelvic Digital Health System leads to more significant improvements in pelvic floor muscle performance than a home PFME program. • Evaluate the contribution of the Digital Health Platform in adherence and treatment of SUI for long term maintenance therapy. HYPOTHESIS: The Digital Health Platform improves adherence to a long-term maintenance program of pelvic floor muscle exercises.
Summary of Study Design:	A prospective, randomized, nested study. Screening of subjects will occur in up to 1 study visits to determine study eligibility. Subjects will be randomized to Kegel exercises (control group) or study device/digital health system use (treatment group). Subjects randomized to the treatment group will be further randomized to follow up with digital reminders or follow up without digital reminders after 8 weeks of leva Plus use. Up to 225 subjects (inclusive of all sites) meeting inclusion/exclusion criteria at Screening will complete a baseline assessment including pelvic examination, evaluation with the PFDx Device and a packet of validated surveys and will then complete 8 weeks of training either with a study device (the treatment group) or with Kegel exercises (the control group) to improve the strength of their pelvic floor muscles. All subjects will return to the clinic to complete a packet of surveys to assess improvements in the symptoms of their urinary incontinence at week 4 and undergo a pelvic floor

	muscle assessment using the PFDx device to measure pelvic floor movement. All subjects will return to the clinic for an end-of-study visit at week 8 including a pelvic floor assessment using the PFDx device to measure pelvic floor movement, physical examination, and complete a packet of surveys. Follow up emails or mailings for additional survey completion will occur 6 and 12 months after the study.
Blinding:	Examiners at study visits will be blinded to randomization
Number of Subjects:	Up to 225 subjects (inclusive of all sites) meeting inclusion/exclusion criteria at Screening visit will return to the clinic to participate in the treatment phase of the study.
Study Treatment:	*Ieva* Plus Pelvic Digital Health System™
Key Assessments:	The following analyses will be performed: **Efficacy:** • *PFDx device* pelvic floor muscle evaluation • *Voiding diary* • Brinks Score • Survey evaluations of incontinence including: o MESA o PFDI o WHODAS o PISQ-IR o McGill Pain Questionnaire o SESPPFE o Patient Global Impression of Severity (PGI-S) Scale o Patient Global Impression of Improvement (PGI-I) o PFIQ **Safety and Tolerability:** o Subjects will be monitored for adverse events and serious adverse events.

4 STUDY EVENTS FLOW CHART

Intervention and outcomes	Screening Visit	Baseline	4 weeks	8 weeks	6 months	12 months
Eligibility and informed consent	x					
Urine Pregnancy Test (if indicated)	x					
UDI-6	x					
Medical History	x	*				
MESA questionnaire	x					
POP-Q	x#			x		
Brinks Scale		x*		x		
Primary Outcome Measures (PFDI, PGI-I, PGI-S)		x	x	x	x	X
PFDI, WHODAS, PISQ-IR, McGill Pain Questionnaire SESPPFE, PGI-S, PGI-I, PFIQ		x	x	x	x	X
PFM performance assessment (PFDx)		x	x	x		
3-day voiding diary	x (before baseline visit)			x		
CGI-S, CGI-I	x			x		
Complications			x	x		
Follow up questions detailing further treatments for SUI					x	X

*May be done at screening visit if < 3 months prior to baseline visit
May be from a visit within 3 months of baseline visit.

5 ABBREVIATIONS

AE	Adverse event
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CRF	Case Report Form
CRU	Clinical Research Unit
EOS	End of Study

FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MESA	Medical, Epidemiologic and Social Aspects of Aging
N	Number of subjects
PFDI	Pelvic Floor Distress Inventory
PFIQ	Pelvic Floor Impact Questionnaire
PGI-I	Patient's Global Impression of Improvement
PGI-S	Patient's Global Impression of Severity
PI	Principal Investigator
PISQ-IR	Pelvic Organ Prolapse/Incontinence Sexual Questionnaire
POP-Q	Pelvic Organ Prolapse- Quantitative
QA	Quality Assurance
QUID	Questionnaire for Female Urinary Incontinence Diagnosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SESPPFE	Self-Efficacy Scale for Practicing Pelvic Floor Exercises
UAE	Unexpected adverse event
US	United States
WHODAS	World Health Organization Disability Assessment

6 BACKGROUND

Pelvic floor muscle exercises (PFME), also known as Kegel exercises, are the first line conservative treatment for pelvic floor disorders, specifically stress urinary incontinence(SUI) within the urogynecology community. Studies have shown that performing PFME and/or pelvic floor physical therapy (PFPT) is the most effective non-invasive treatment for SUI. Some women have trouble identifying and contracting the correct muscles when performing PFME. The leva Pelvic Digital Health System ™ is an innovative device that allows women to have real-time visual verification that PFME is performed correctly and consistently by guiding women through pelvic floor muscle lifting. The leva Pelvic Digital Health System ™ also measures and records the results of every PFME session performed while using the device thus encouraging patient compliance. Data generated during exercise is transmitted to a safe, HIPAA compliant database in a cloud, from which an algorithm used to evaluate adherence can be used to provide automatic reminders and education via text message to encourage participation. In the proposed study we hypothesize that the leva Digital Health Platform:

- improves adherence to a long-term maintenance program of pelvic floor muscle exercises.
- leads to more significant improvements in pelvic floor muscle performance than a home PFME program.

There are other alternative biofeedback devices that are home-based and approved by the FDA, however these are expensive and may not be covered by insurance. There is no research to demonstrate that these devices are better than a PFME with or without supervision of a pelvic floor Physical Therapist. The *leva* device has a unique way of verifying muscle contraction that is not focused on strength, but rather vertical displacement with muscle contraction.

7 STUDY OBJECTIVE AND ENDPOINT

7.1 Study Objective

Primary objectives:

- Compare the efficacy of using an innovative intravaginal system (Ieva® Digital Pelvic System™) to perform pelvic floor muscle exercises (PFME) compared to a Kegel exercise home program in women with stress-predominant urinary incontinence (SUI).
  HYPOTHESIS: The Ieva® Plus Pelvic Digital Health System is superior to a home PFME program in the treatment of stress-predominant urinary incontinence.

- Compare the effect of the Leva® Plus Pelvic Digital Health System with home PFME program on measures of pelvic floor muscle performance
  HYPOTHESIS: The Ieva® Plus Digital Pelvic System leads to more significant improvements in pelvic floor muscle performance than a home PFME program

- Evaluate the contribution of the Digital Health Platform in adherence and treatment of SUI for long term maintenance therapy.
  HYPOTHESIS: The Digital Health Platform improves adherence to a long-term maintenance program of pelvic floor muscle exercises.
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7.2 Study Endpoint(s)

Efficacy:

Efficacy, the primary outcome will be evaluated following 8- weeks of treatment at an in-person interview by study personnel blinded to randomization, and then again by phone and email or mail at 6- and 12- months. Two validated measures will be used to evaluate primary outcomes. First, the patient global impression of improvement (PGI-I), with success was defined as a response of “much better” or “very much better”. Second, the Pelvic Floor Distress Inventory (PFDI-20) urinary distress inventory (UDI-6), with success defined as the absence of bothersome stress incontinence symptoms as indicated by an answer of “no” to the stress incontinence subscale items OR a response of “yes” but with a bother of “not at all” or “somewhat. Other responses will not be considered successes.

Safety and Tolerability:

1. Reported Adverse Events (AEs) and Serious Adverse Events (SAEs)

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

- A prospective, nested, randomized multicenter controlled study to evaluate the efficacy of using the leva® Plus Digital Pelvic System to perform PFME in comparison to Kegel exercises.
- Subjects will be patients referred to a Urogynecologist's office for evaluation.
- Following completion of baseline screening and consent, patients will be randomized by study coordinators at the baseline office visit using an automated randomization system.
- Patient population: women with moderate to severe SUI or stress-dominant mixed urinary incontinence.
- The duration of participation is 8- weeks, with expected post-intervention follow up surveys 6- and 12-months after study terminus.
- Up to 75 participants per site will be enrolled for a total of 225 subjects in the trial.

STUDY ENROLLMENT
The women interested in the study will be screened for participation based on inclusion/exclusion criteria and the MESA questionnaire identifying stress or stress-dominant mixed incontinence, and the UDI-6 (score > 25).

Screening visit: The study will be explained by the study staff and the consent will be reviewed with prospective participants.

1) The following questionnaires will be administered:
    a. MESA
    b. UDI-6
2) Pelvic exam will be performed including:
    a. POP-Q (acceptable to report from an exam within 3 months of baseline)
    b. Pelvic floor muscle assessment (Brink Scale) (may be performed at baseline or screening visit (if screening < 3 months prior to baseline)
3) If the eligibility requirements are met, patients should be given a 3-day voiding diary (acceptable if reported within 3 months of baseline visit)

The consent will be obtained by the licensed physician investigators or study assistants. Study participation will be entirely voluntary.

STUDY PROCEDURES
Once patients have undergone the appropriate screening evaluation, met criteria for study participation, and provided informed consent, subjects will be randomized to one of two study arms. The "Kegel" arm will involve patient education and performance of Kegel exercises, the current standard of care. The "Leva" arm of the study will undergo patient education and performance of pelvic floor muscle exercises using the Leva system. Subjects in the "Leva" arm will be sub-randomized to one of two long term follow up plans, follow up without reminders or follow up using automated reminders by text message.

Subjects will complete validated standardized quality of life questionnaires and pelvic floor muscle testing using the PFDx device at in-office visits at baseline, 4 weeks and 8- weeks. They will record 3-day voiding diaries at baseline and at 8-weeks. Beyond 8- weeks subjects will be asked to participate in follow-up calls at 6 and 12 months and complete validated standardized quality of life questionnaires by mail or email. Patients who were randomized to the Leva arm of the study and were sub-randomized to the "follow up reminder" will receive weekly reminders to perform their pelvic floor exercises using the Leva device

The study will be funded by Renovia, who will provide leva Plus and PFDX devices for the study and subject re-numeration.

$50 for the baseline visit with the study team
$50 for the 4-week follow up visit
$100 for the 8-week final study visit
$50 for the completion of >80% of the study exercises
$50 upon completion and return of surveys at 6 months
$50 upon completion and return of surveys at 12 months.

Please note that $300 compensation is provided for every subject who completes the study in its entirety. This compensation level will increase to $350 for those subjects in either arm who attest to completion of >80% of the study exercises.

Initial payment will occur by the site and in a manner consistent with individual site policy after the completion of the 8-week final study visit. Compensation will occur immediately following the return of completed 6-month and 12-month surveys.

If the subject leaves study early, the subject will receive a pro-rated amount based on the study milestones completed. Subjects will be compensated $25 for unscheduled return visits.

Subjects will be reimbursed for parking costs associated with their visits.

Visit #1 – Baseline visit - the participants will undergo the following procedures:

Following completion of baseline evaluation and consent, patients will be randomized by study coordinators at the baseline office visit using an automated randomization system.

1) Medical history including GYN history, OB history, medical diagnoses, medications, and prior surgical procedures.

2) Questionnaires:
a. PFDI
b. PISQ-IR
c. McGill Pain Questionnaire
d. SESPPFE
e. Patient Global Impression of Severity (PGI-S) Scale
f. WHODAS

g. PFIQ

3) Voiding diary – collection of a 3-day intake and output and symptoms diary completed *before* baseline visit

4) Health Care Provider will perform a Pelvic Organ Prolapse Quantitative (POP-Q) assessment (If not completed at screening)

5) The PFDx device will be then used to measure the pelvic floor angles and strength. This will be supervised by clinical research personnel blinded to randomization.

6) To optimize blinding to arm, the randomization will occur following the above surveys and evaluations.

Following randomization, the subject will participate in one of two main study arms:

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KEGEL STUDY ARM

- Subjects randomized to the Kegel Arm will receive standardized written and verbal instructions on how to perform three times daily/7 days per week pelvic floor muscle exercises and their ability to perform the correct muscle action will be confirmed by physical exam (written instructions per the handout, adapted from Voices for PFD). They will be instructed to perform these exercises three times daily throughout the 8-week study period, based on a commonly used kegel regimen. These instructions will occur during the baseline visit. Also at the baseline visit, subjects will be informed they will be asked to attest to the fact that they performed these exercises twice daily at least 80% of the time (approximately 17 times per week). This attestation will ask the subject to recall their adherence; no diary or other record will be required.
- Subjects will return to the office on week 4 to participate in validated questionnaires and undergo a progress evaluation using the PFDx. For clinical questions they will be directed to follow up with their physician. Their evaluator will be blinded to their randomization.
- Subjects will return to the office on week 8- to participate in validated questionnaires, undergo progress evaluation using the PFDx, and physical examination including a POP-Q and Brinks score, and attest to their adherence. Their evaluator will be blinded to their randomization
- Following week 8, patients will be recommended to continue weekly Kegel exercises, but will be free to pursue alternative treatments if desired. They will participate over the phone and via email or mail in validated questionnaires, in addition to reporting what (if any) additional therapies they have undergone for treatment of stress urinary incontinence at 6 months and 12 months after baseline.

LEVA STUDY ARM

- Subjects randomized to the leva® Plus Pelvic Digital Health System will receive training on the use of the Leva® Plus Digital Health System including installation of the Digital Health System app, the completion of a training module, a timed lift test and one full leva exercise session of five timed lifts. Training will occur at the baseline visit. Subjects will be instructed to perform the lifts twice a day, for 2 ½ minutes each session, 7 days a week for a total of 8- weeks. Subjects will be informed they will be asked to attest to the fact that they performed these exercises twice daily at least 80% of the time (approximately 11 times per week). This attestation will ask the subject to recall their

adherence; no diary or other record will be required, although they will also be informed that the leva digital system tracks adherence. During the study period (8-weeks) subjects with the leva will contact the Renovia Patient Care Engagement team with any technical questions or issues regarding leva use. They will receive regular (6 days/week) text messages based on their performance of pelvic floor muscle exercises using the Leva device using predetermined algorithm for content. For any clinical questions they will be directed to their physician's office to speak with a healthcare provider.

- Subjects will return to the office on week 4 to participate in validated questionnaires (see chart) and undergo progress evaluation using the PFDx device. For clinical questions they will be directed to follow up with their physician. Their evaluator will be blinded to their randomization.
- Subjects will return to the office on week 8 to participate in validated questionnaires (see chart) and undergo progress evaluation using the PFDX device and physical examination including a POP-Q and Brinks score, and attest to their adherence. Their evaluator will be blinded to their randomization.
- Following week 8, patients will be recommended to continue weekly pelvic floor muscle exercises using the leva device but will be free to pursue alternative treatments if desired. Based on initial sub-randomization, subjects will receive periodic standardized text messages reminding them to use the leva over the next 10 months or receive no additional contact via the leva device.
- At 6- and 12- months they will participate in validated questionnaires (see chart) by phone and email or mail, in addition to reporting what (if any) additional therapies they have undergone for treatment of stress urinary incontinence at 6 months and 12 months after baseline.
- The third party research center will provide a single phone call to the subjects receiving the leva plus to ensure the device is functioning properly. If there are questions regarding the device function, a conference call will be undertaken to allow the subject to trouble-shoot device function with the sponsor technical specialist. The sponsor will at no time posess protected health information (PHI)

VISIT CONTENT

At week 4 all study participants will return to the office to undergo a PFDx evaluation of pelvic floor muscle function and complete and return the following questionnaires:

a. PFDI
b. PISQ-IR
c. McGill Pain Questionnaire
d. SESPPFE
e. Patient Global Impression of Severity and improvement (PGI-S, PGI-I) Scale
f. WHODAS
g. PFIQ

At week 8 all study participants in both arms will return to the clinic for the PFDx device evaluation of pelvic floor muscle function and physical examination including a POP-Q and Brinks score, and the following questionnaires:

a) PFDI
b) PISQ-IR
c) McGill Pain Questionnaire
d) SESPPFE

e) PGI-S and PGI-I
f) WHODAS
g) PFIQ
h) Attestation of 80% or greater compliance with exercises twice daily as per protocol

The 6 and 12 months follow-up by phone and email or mail will include:

i) PFDI
j) PISQ-IR
k) McGill Pain Questionnaire
l) SESPPFE
m) PGI-S and PGI-I
n) WHODAS
o) PFIQ

PFDx device pelvic floor muscle evaluation for both study arms will include:

- Baseline pelvic floor muscle vaginal angle (at rest)
- Pelvic floor muscle vaginal angle with Valsalva
- Pelvic floor muscle angle with relaxation
- Pelvic floor muscle angle with muscle contraction
- Number of repetitions of contraction in 15 seconds;
- Maximum time a subject can sustain a pelvic floor muscle contraction.

This evaluation will be conducted using the PFDx device placed in the vagina by the subject and conducted by study staff using an automated measurement protocol.

8.1.1 Confinement and Return Visits

The screening and baseline visit may be combined into one visit and take up to 1.5 hours. The visit at 4 weeks may take up to 1 hour. The end-of-study visit may take up to 1.5 hours. There are no other scheduled visits for this study. Follow up phone calls may take up to 45 minutes. See Study Events Flow Chart (Section 4).

8.2 Risks and/or Benefits to Subjects

***leva* Incontinence System**

The *leva* Incontinence System TM (*leva*) is an FDA-approved, Class II medical device used to help women overcome urinary incontinence. It will NOT be used in this study, but is the predicate device upon which the study devices are based. The device has two main components: (1) a tampon-shaped silicone form that is inserted into the vagina (the *vaginal insert*) and has a cable with a connector at the end; and (2) a control box that connects to the vaginal insert and contains a microprocessor and Bluetooth radio (the *control box*). The intravaginal device contains six accelerometer sensors placed on a flexible circuit board that is encased in a silicone form. The control box reads

Figure 1. Ieva Incontinence System

positional information from the six sensors in the vaginal insert and communicates that data to a mobile phone application (the *App*).

The *Ieva* Incontinence System ™ has been tested and found to conform with the requirements of IEC 60601-1:2005 (3RD Edition), Medical Electrical Equipment-Part 1: General requirements for basic safety and essential performance; IEC 60601-1-2:2007, Medical electrical equipment-Part1-2:General requirements for basic safety and essential performance-Collateral standard: Electromagnetic compatibility-Requirements and tests; and IEC 60601-1-1-11, General requirements for basic safety and essential performance-Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment. The results of these tests indicate that the device is safe for its intended use. In addition, a biocompatibility evaluation was performed to satisfy ISO 10993-1 and FDA requirements. All patient contacting materials have been tested, and passed cytotoxicity, sensitization and irritation or intra-cutaneous standards.

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***Ieva* Plus Incontinence System**

The *Ieva Plus* Incontinence System ™ is a next-generation device currently under development. It has the same Indications for Use and Intended Use as the *Ieva* Incontinence System ™. The primary differences between *Ieva* and *Ieva Plus* are as follows: (1) the *Ieva Plus* device combines the vaginal insert and control box into a single, smaller form that eliminates the need for a cable; (2) the *Ieva Plus* device has a small, detachable battery pack at the base; (3) the *Ieva Plus* device is made of a biocompatible thermoplastic elastomer, whereas *Ieva* is made of biocompatible silicone; and (4) the *Ieva Plus* device uses a Bluetooth Low Energy radio whereas the *Ieva* devices uses a classic Bluetooth radio. The *Ieva Plus* device communicates with an iPhone or Android mobile phone and provides biofeedback to the patient in the same way that *Ieva* does.

Ieva Plus Inco

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The *Ieva Plus* device has not been submitted to FDA for approval yet. However, it is being developed under appropriate Design Controls and Risk Analysis, as defined by FDA's 21 CFR 820 and ISO 13485. Renovia plans to submit a 510k application to FDA by late summer 2017. Given the similarity of *Ieva Plus* and *Ieva*, along with independent risk analysis, *Ieva Plus* is considered a "non-significant risk device" as defined by 21 CFR 812.3(m).

PFDx

The *PFDx* device is an investigational medical device currently used to gather data related to pelvic floor health. It uses

PFDX device

substantially equivalent technology to the *Ieva* Incontinence System, an FDA-approved, Class II medical device. Whereas the *Ieva* device uses 6 accelerometer sensors, the *PFDx* device uses 12 sensors, allowing for a more complete evaluation of a woman's physiology. The *PFDx* device is shaped as a ring that sits in the fornix with a thin, flat strip that descends along and out of the vagina. At the end of the device (outside the woman's body) is a small enclosure that houses a microprocessor and a Bluetooth Low Energy radio. The *PFDx* communicates wirelessly to a laptop or mobile phone, in a similar manner to the *Ieva* device. All sensors related components are over-molded with the same biocompatible silicone material used to manufacture the *Ieva* device. Given the similarity of *Ieva Plus* and *Ieva*, along with independent risk analysis, *Ieva Plus* is considered a "non-significant risk device" as defined by 21 CFR 812.3(m).

8.3 Selection of Study Population

8.3.1 Inclusion Criteria

Subjects must fulfill all the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

- Female.
- Capable of giving informed consent.
- Self-reported stress-type UI symptoms of >= three months duration
- Diagnosis of stress predominant urinary incontinence based on MESA stress symptom score greater than MESA urge symptom score (percent of total possible urge score).
- UDI-6 score >/= 25
- Willing to participate in the 8-week study with follow up at 6-and 12-months, refraining from the pursuit of treatment for Stress Urinary Incontinence using other modalities (i.e. will not wear a pessary, participate in pelvic floor PT or surgery) during the first 8- weeks.

8.3.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

- Absence of a vagina.
- Age <18 years.
- Stage 3-4 pelvic organ prolapse (as determined by POP-Q).
- Diagnosis of any neuromuscular disease.
- Non-ambulatory.
- Currently pregnant or <12 months post-partum.
- </= 3 months after failed surgery for stress urinary incontinence.
- Previous pelvic floor muscle training (PFMT) within the last 12 months under a supervised therapeutic plan of care.
- Currently taking, or has taken within the last 2 months, medication to treat urinary incontinence.
- Prior augmentation cystoplasty or artificial sphincter.
- Implanted nerve stimulator for urinary symptoms.

- Participation in another clinical study within 30 days of screening.
- Impaired cognitive function.
- Contraindication to the use of a vaginal probe.
- Unable to understand instructions on the use of the Ieva® Plus Pelvic Digital Health System.
- Unable to actively recruit the pelvic floor muscles to any degree for attempted volitional contraction.

8.3.3 Removal of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI in consultation with the Sponsor for the following reasons:

- Subject is unable to use the *Ieva* device;
- Subject experiences a SAE;
- Protocol violation.

The clinical report will include reasons for subject withdrawals.

8.3.4 Prohibitions and Concomitant Therapy

There are no prohibited therapies, activities or medications except as described in the exclusion criteria. All medications taken by subjects during the study will be recorded.

8.4 Treatments

8.4.1 Treatment Administered

Subjects will train twice daily for 8- weeks using the *Ieva* device (for the treatment group) or Kegel exercises (for the control group).

8.4.2 Treatment Compliance

The *Ieva* device sends deidentified subject training and testing data to a secure, HIPAA compliant database, and subjects will receive periodic text messaging with training trips, reminders and motivational messages. Those in the Kegel control group will not be monitored for treatment compliance.

9 STUDY PROCEDURES

The Study Events Flow Chart (Section 4) summarizes the procedures to be performed at each visit. Individual procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.1.1 Adverse Events

9.1.1.1 Monitoring

Subjects will be monitored at each study visit for adverse events. A specific enquiry will be made at the time of each check-in. The subjects will be queried with an open-ended question such as “How are you feeling?” or “How have you been feeling since your last visit?”

9.1.1.2 Serious Adverse Event

Any SAE will be reported to the Sponsor and the Institutional Review Board (IRB), as required. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed study treatment-related and within 5 working days to the IRB (24 hours of discovery if the event involves a death), as required.

An SAE is any AE or suspected adverse reaction that in the view of either the PI or Sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Treatment of SAEs will be performed by a physician, either at the site or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

If a SAE occurs to a subject on this study, contact the Sponsor’s Representative listed in Section 2.

10 DATA ANALYSIS

Data will be handled and processed according to Operating Procedures, which are based on the principles of GCP.

10.1 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the Clinical Study Report.

10.1.1 Determination of Sample Size

This planned randomized controlled trial is a tertiary prevention trial, comparing the efficacy of the Leva device in the treatment of stress urinary incontinence to standard pelvic floor muscle training, consisting of office education and a home exercise program. Our primary outcome is the proportion of subjects who are very much better/much better as measured by the PGI-I. Sample size for 20% difference between groups given a 30% success rate of home exercise programs, alpha=0.05, and a power of 0.8, the needed sample size is 93 patients in each arm. Allowing for an attrition rate of approximately 15%, we require approximately 225 patients.

10.1.2 Subjects to Analyze

Safety Population: All subjects who were administered at least one training session will be included in the safety evaluations.

Efficacy Population: All subjects who had at least one *leva* testing administration and measurement of any of the efficacy assessments post Screening Visit.

10.2 Safety Evaluation

Safety data will be populated in individual CRFs. All safety data will be listed by subject.

AEs and SAEs will be monitored throughout the study. All SAEs will be recorded and reported. Concomitant medications and medical history will be listed by subject.

11 STUDY ADMINISTRATION

11.1 Ethics

11.1.1 Institutional Review Board

This protocol will be reviewed by the institutional review boards of the participating institutions,

11.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50 and 56, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

11.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to Screening and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their ICF.

11.2 Termination of the Study

The Principal Investigator reserves the right to terminate the study in the interest of subject welfare. The Sponsor may terminate the study for administrative reasons.

11.3 Data Quality Assurance

The Principal Investigator will designate personnel responsible for implementing and maintaining quality assurance and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

11.4 Direct Access to Source Data/Documents

The Principal Investigator will ensure that the Sponsor, IRB and domestic and foreign regulatory authorities will have direct access to all study sites, source data/documents, and reports for monitoring and auditing. If other study-related monitoring should be done by other parties, those parties will be required to sign a confidentiality agreement prior to any monitoring or auditing.

11.5 Study Device Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of devices to allow completion of this study. Each subject in the “Ieva” arm will be provided with her own device and may retain the device at the end of the study. The Cost of goods value of the device is less than $100. If

the subject does not already own an iPhone or android phone to run the *Ieva* software, they will be provided an alternative at no cost. It will be up to the discretion of the Sponsor if the alternative device needs to be returned to the study site or can be retained by the subject at the end of the study. Records will be made of the receipt and dispensing of devices supplied. This accountability record will be available for inspection at any time. At the completion of the study, the original accountability record will be available for review by the Sponsor upon request.

11.6 Data Handling and Record Keeping

All raw data generated in connection with this study, together with the final report, will be retained for at least 5 years after completion of the final report. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

11.7 Publication Policy

All unpublished information given to the Principal Investigator by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.