RANDOMIZED CONTROLLED STUDY OF EFFICACY OF ELITONE DEVICE FOR THE TREATMENT OF MILD-MODERATE STRESS URINARY INCONTINENCE IN WOMEN

Supported by: Elidah, Inc.

Study Intervention Provided by: Elidah, Inc. 810 Main St. Ste. C, Monroe CT 06468

Sponsor of IND (IDE): Electrodes are a Non-significant risk device. No IDE required.

Version Number: 1
Version Date: July, 19, 2018
Summary of Most Recent Revision: N/A – New release

NCT#: NCT03782116

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY.

1.1 Study Title

Randomized controlled study of the efficacy of Elitone Device for the treatment of mild-moderate urinary incontinence in women.

1.2 Objectives

The primary objective of this study is to demonstrate the safety and efficacy of the Elitone device as a conservative treatment for stress urinary incontinence.

1.3 Design and Outcomes

This is a randomized controlled study in which subjects are assigned to either a treatment group or a control (sham) group. Pre- and post-study outcome measures evaluate the change in incontinence episodes on women with mild-moderate stress urinary incontinence.

1.4 Interventions and Duration

Study participants in the treatment group will receive surface electrical stimulation intended to treat incontinence. Participants in the control group will receive non-therapeutic surface electrical stimulation. Treatment is self-administered in an at-home environment according to a defined schedule. Outcomes are assessed after 12 weeks.

1.5 Sample Size and Population

The population includes women ages 21-75 with mild-moderate stress urinary incontinence. The active and control groups will be enrolled in a 2:1 ratio, totaling 40 and 20 subjects respectively.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

The primary objective of this study is to demonstrate the safety and efficacy of the Elitone device as a conservative treatment for stress urinary incontinence.

2.2 Primary Endpoint

Treatment efficacy is assessed by comparing the average number of stress urinary incontinence episodes per day at the end of treatment to the corresponding pre-treatment number.

Safety is determined by review of Adverse Events as defined in 7.3, and determination of no serious adverse event during the study.

2.3 Hypothesis

The null hypothesis reads: *The number of subjects treated with Elitone who achieve a clinically meaningful reduction (≥50%) in stress urinary incontinence episodes per day against baseline is not different than the control group.*

The alternative hypothesis is that: *The number of subjects treated with Elitone who achieve a clinically meaningful reduction (≥50%) in urinary stress incontinence episodes per day against baseline is statistically significantly greater than the number who do so in the control group.*

2.4 Secondary Objectives

The secondary objectives are to characterize the device's efficacy at improving continence based on other meaningful clinical endpoints. This data may be useful to support future product marketing claims including support for over-the-counter use and mixed/urge incontinence. Further, certain information may inform opportunities for future product improvements.

2.5 Secondary Endpoints:

Endpoints that support the secondary objectives are listed below. Further description is provided in 5.3 and 9.5.

- 24h Pad Weight Test
- Incontinence Quality of Life score (I-QoL)
- Pads per Day
- Urge Incontinence Episodes or Bathroom Visits per Day
- Usability Data (e.g. Ease of Use, Satisfaction, Preferred Intensity Settings)

3. BACKGROUND AND STUDY RATIONALE

3.1 Background on Condition, Disease, or Other Primary Study Focus

Urinary incontinence (UI) is a widely prevalent condition affecting approximately 1 in 3 women over the age of 30, and 1 in 2 women over the age of 50.[1,2,3] Although a very private concern, it has far-reaching physical, psychological, social, and economic implications. For example: UI has been found to reduce health-related quality of life measures, with a strong correlation with depression,[4] UI is the number one reason for entry into nursing homes, and the annual cost to Medicare has been estimated at $10 billion, and at $20 billion for the entirety of the US healthcare system. 75% of these women are specifically affected with Stress Urinary Incontinence (SUI), which is the loss of continence due to weakened pelvic floor muscles, resulting from a variety of factors including child-bearing, athletic pursuits, trauma, and aging.[5,6,7] Their urine leakage occurs when physical exertion (e.g. sneezing, lifting, running) increases intra-abdominal pressure. There are no medications that address SUI, and while surgery can provide relief, it is painful, expensive, and requires hospitalization and multiple weeks of recovery. Additionally, often women do not want the medication that is available for Urge Urinary Incontinence (UUI) due to potential interference with other medications.

Non-surgical strengthening of the pelvic floor muscles has proven effective in treating most SUI and is first-line treatment for UUI[8], and this is typically achieved through Kegel exercises, biofeedback, weighted cones or intravaginal electrical muscle stimulation (EMS). However, subjects routinely struggle to perform Kegel exercises correctly or with sufficient frequency (3x/day for 3-6 months) which leads to low compliance. Introducing intravaginal devices or an intravaginal probe necessitates a private location and dedicated treatment time (often at a treatment center), further challenging the likelihood of adoption.[5,9,10,11]

To complicate matters, 4 out of 5 sufferers do not speak with their primary care physician until symptoms have intensified and persisted for numerous years (6.5 years on average), and others do not consult a specialist (i.e. urologist) because they fear the recommendation of surgery.[10] This leads to two thirds of affected women suffering quietly without treatment while conditions worsen.[12] Thus, the need exists for a non-surgical means of strengthening the pelvic floor muscles that has a higher rate of patient adoption and compliance than current solutions.

3.2 Study Rationale

There is a long history of use of intravaginal EMS for treatment of SUI, and it is predicated on the assumption that proximity of the electrodes to the pelvic floor muscles is of primary importance. This is largely accurate. However, appreciating that subjects who seek help most often ultimately fail treatment due to adoption and compliance issues, it is equally important to consider whether the psychological or physiological barriers associated with intravaginal EMS offset any benefit from the treatment's intimate electrode placement.

Several recent clinical reports suggest that a pattern of surface electrodes placed in the suprapubic and ischial tuberosity regions are as effective as intravaginal electrodes at retraining the pelvic floor muscles.[13] In these studies, treatment was administered by a clinician who placed four separate electrodes on the defined tissue region and delivered prescribed pulse waves during regular training sessions. Unfortunately, the need to deliver this treatment in a clinical environment makes it burdensome to the patient and the health system.

Building on these findings, Elidah has developed a wearable, SUI specific EMS device configured for application by the patient and for use outside the clinic, allowing treatment at home and potentially accelerating the rate and efficacy of muscle retraining.

Surface electrodes have been used for EMS and transcutaneous electrical nerve stimulation (TENS) applications since the 1970's. They have an established history of safe and efficacious across a range of anatomic application sites, and the FDA considers electrodes to be low risk devices: "*Electrodes are a Non-significant risk device, no IDE needed" (Non-implantable Electrical Incontinence Device).*[14]

Elidah has conducted clinical trials of similar design (WIRB 20162650), and using the same or similar devices (WIRB 20180640), and observed clinically meaningful improvements in incontinence symptoms without serious adverse events. The current protocol is intended to expand on that earlier work through controlled study that closely replicates real-world use of the device.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

All subjects must meet the inclusion criteria below to participate in this study. Any waiver of these inclusion criteria (or the subsequent exclusion criteria) must be approved by the Clinical Director on a case-by-case basis prior to enrolling the subject, and documented in the subject's Case Report Form (TR-1131-FORM-10).

- Predominant stress urinary incontinence as determined by responses to a series of three standard questions from the King's Health Questionnaire; specifically:
    - An affirmative response to "Do you lose urine with physical activities such as coughing, sneezing, running?",

    - An affirmative or negative response to “Is it very difficult to control when you have a strong urge to urinate?”,
    - And, if an affirmative response to the second question, a negative response to “Are more of your incontinence episodes due to a strong urge to urinate than to abdominal pressure such as sneezing?”
- Mild-moderate incontinence symptoms as determined by self-reported typical number of accidents of 1 per 24 hours or more. Symptom severity is later verified with data from the Daily Log (See 5.4)
- Age: 21-75y
- Gender: Female

4.2 Exclusion Criteria

Subjects will be excluded from enrollment if they meet any of the following criteria:

- Severe incontinence as determined by self-reported >5 accidents in 24-hr period
- Currently pregnant, may be pregnant, attempting to become pregnant, or delivery within previous 6 weeks
- Implanted cardiac device, untreated cardiac arrhythmia or suffer from other heart problems.
- Cancer, epilepsy or cognitive dysfunction
- Vaginal or pelvic surgery within previous 6 months
- Complete denervation of the pelvic floor
- History or symptoms of urinary retention, extra-urethral incontinence, overflow incontinence
- Active urinary tract infection (UTI) or history of recurrent UTIs (more than three in a year)
- Recurrent vaginitis (bacterial/fungal)
- Pelvic pain/painful bladder syndrome
- Underlying neurologic/neuromuscular disorder
- Severe Obesity as defined by BMI >= 35
- Chronic coughing
- Impaired decision making, drug or alcohol dependence, or suicidal thoughts.
- Anyone who lacks the capacity to consent for themselves or who requires a legal representative to give informed consent.

4.3 Study Enrollment Procedures

The study uses the following multi-step process to achieve enrollment:

Recruitment

- Ads placed in social media and other forums will attract candidates to a website that describes the study.
- Ads will be placed in the US without geographic targeting.
- Ads will be served to candidates using keywords (e.g. “incontinence”).
- Alternately, healthcare providers who become familiar with the study can direct candidates to the study. These candidates will go through the same screening as all candidates and the referring healthcare provider would not be considered a study investigator. It is permissible for the referring healthcare provider to assist the candidates with completion of screening/consent information and to forward the information directly to Elidah.
- TR-1131-FORM-14 identifies the language that will be used in recruitment messaging.

Screening

- Interested candidates complete an online survey comprising Screening Questions (TR-1131-FORM-13)
- Responses are maintained electronically in a Screening Log (TR-1131-FORM-11) which includes candidate contact information, date of survey completion, and survey responses.
- Survey responses will be reviewed to confirm that (based on IP addresses and/or provided contact info) candidates did not complete the survey multiple times with different responses, potentially in an attempt to qualify for enrollment.
- Hardcopy or verbal responses are acceptable and will be manually entered into the Screening Log.

Consent

- Candidates that meet the enrollment criteria based on responses to the screening survey are contacted by Elidah.
- Study personnel describe the study requirements, respond to any questions from the candidate and explain the consent process (see 11.2). Notes of this communication are maintained in the Case Report Form (TR-1131-FORM-10) if enrolled, or in the screening log if not enrolled.
- Consent documentation (TR-1131-FORM-5) is sent to the candidate either electronically or as a hardcopy.
- The candidate returns the signed consent form, or via an online option.
- The candidate is now considered a “subject”, and a sequential Subject Number is assigned (TR-1131-FORM-7).
- A copy of the signed consent document is maintained in the subject’s Case Report File.

Treatment Initiation

- Study materials are sent to the subject for treatment initiation (see 10.1 and 10.2)
- Confirmation of eligibility is based on baseline data per 5.4.

4.4 Recruitment Strategies

Appreciating that achieving enrollment targets in a clinical study can be challenged by various factors, including difficulty in identifying qualified candidates and candidates not wanting to participate in a study in which they may be assigned to a control group, Elidah has implemented several strategies to mitigate such challenges including:

- Recruitment using social media allows access to thousands of women from across the US, which additionally encouraging participation from a diverse pool of candidates.
- The active to control enrollment ratio is 2:1, giving subjects a greater chance of being assigned to a group that will realize a clinical benefit.
- Subjects in the control arm will optionally be allowed to pursue 6 weeks of treatment with the active device after completion of the control study requirements. Although the subject may elect to monitor and report her experience with the active device, such data will not be included in the analysis of the primary endpoint.

4.5 Retention Strategies

- Subjects who complete the study will be paid $200 in cash or equivalent gift card. If the subject does not complete all study requirements the Clinical Director has discretion to compensate with a lesser amount.
- Subjects will be contacted after the 1st, 6th and 12th weeks to confirm ongoing participation and to provide the opportunity for subjects to ask questions.
- Subjects will have the option to download a mobile app that can keep track of progress of intensity level, days used, and leaks (if they enter it). This would not replace the diary.

5. STUDY DESIGN & PROCEDURES

5.1 Study Type

Randomized, controlled, prospective clinical study. Subjects will be assigned to the arms (i.e. treatment and control groups) in a 2:1 ratio.

5.2 Number of Subjects

An analysis of statistical power determined that 40 subjects in the active group and 20 subjects in the control group is likely sufficient to achieve statistical significance with respect to the primary outcome measure. Appreciating that some subjects who are initially enrolled will fail to complete treatment and return the study materials, it is likely that 70-80 subjects will be enrolled. See 9.1 for discussion of the sample size calculation.

5.3 Description of Evaluations

This research utilizes validated methods for evaluating the clinical impact of the device/treatment, including several identified in the FDA guidance document regarding clinical studies that investigate urinary incontinence.[15] Stress urinary incontinence episodes per day data, obtained from the subject's Daily Log, serves as the primary efficacy outcome measure (see 2.2). Analysis of adverse events serves as the primary safety outcome measure (see 2.2). Evaluations utilized throughout the study are described below. See 9.5 for detail regarding strategies for analyzing the data obtained in these evaluations.

- **I-QoL Questionnaire** (Pre- and Post-study) – the Incontinence Quality of Life (I-QoL) questionnaire is validated tool for assessing changes in the degree to which urinary incontinence affects a woman's quality of life (TR-1131-FORM-2). It comprises 22 questions, to which the subject provides a numeric response on a 1-5 scale. The score is the sum of the numeric responses, which can range from 22 to 110. A change of 2.5 points is considered clinically significant.[15] The I-QoL questionnaire is provided to the subjects as part of pre- and post-study materials. Completed questionnaires are returned to Elidah via mail or electronically (see 10.4).
- **24-Hour Pad Weight Test** (Pre- and Post-study) – This test is used to quantify the volume of urine leakage. The subject wears an absorbent pad(s) over a period of 24 hours, after which the pad(s) are weighed to determine the mass of any leaked urine. A reduction of ≥50% compared to a baseline measure is considered clinically significant. A mass of less than 1.3g is considered to be "dry", i.e. no leakage.[16] Pre-weighed pads will be sent to the subjects as part of the study materials. During pre- and post-study assessments the subjects will wear the pad(s) for 24 hours, seal the pad(s) in a moisture proof bag, and mail to Elidah for weighing. Note that although this assessment does provide an objective

measure of change in leakage volume, the method is known to be subject to variability, may not be meaningful to patients, and requires subject compliance.[15] For this reason, Elidah has identified this tool as a secondary outcome measure and does not intend to use the data as a primary means for establishing device efficacy.

- **Pre-Study Incontinence History and Usability Questionnaire** (Pre-study) – Included in the pre-study activity is a questionnaire that investigates each subject's medical history as it pertains to incontinence as well as their perceptions and preferences regarding incontinence treatments (TR-1131-FORM-1). Some of this information may be utilized in post hoc subgroup analysis (see 9.5). It may also be useful in informing strategies for Elidah to effectively reach potential patients.
- **Daily Log** (Baseline week and treatment weeks) – Subjects are required to maintain a Daily Log throughout the study (i.e. baseline week through 12th week). Among other items they log their treatment completion (Y/N), treatment intensity (0-35), number of incontinence episodes, and number of pads used (TR-1131-FORM-3). The log also provides space for the subject to add notes that may be relevant to subsequent analysis. The log is maintained by the patient in hardcopy and returned to Elidah at the end of the study for analysis (see 10.4). Alternatively, an equivalent electronic form may be utilized. The stress urinary incontinence episodes per day data will serve as the primary outcome measure (see 9.5). See 9.5 regarding handling of missing information, particularly as it relates to the weeks between the baseline and 12th week.
- **Post-Study Usability Questionnaire** (Post-study) – At the end of the study subjects are asked for feedback regarding any perceived improvement in continence, their satisfaction with the treatment, the ease of use, and other issues that may inform opportunities for future device/treatment improvements (TR-1131-FORM-4).
- **Adverse Events** (Throughout Study) – See 7.3.

5.4 Protocol Schedule

The study comprises five stages: Pre-study, Baseline, Verification, Treatment, and Post-Study.

- **Pre-Study** –The subjects initiate pre-study activity, which includes completion of the I-QoL Questionnaire, the Pre-study Incontinence History and Usability Questionnaire, and the 24-hour pad weight test. The subject mails the pre-study materials back to Elidah. There is no difference in requirements between the two study arms.
- **Baseline** –Concurrently, the subjects maintain the Daily Log for 7 days to establish a baseline of the episodes/day and pads/day measures. No treatment is administered during this period. After 7 days the subjects submit the data to Elidah (electronically or hardcopy). Subjects are instructed that they should not perform baseline activity during menses or if they are ill. Note that it is acceptable to complete or return the pre-study materials throughout this 7 day baseline period. There is no difference in requirements between the two study arms.
- **Verification** - If the 7 day baseline shows that the subject does not qualify based on urinary stress incontinence episodes, then the subject will be disqualified and the device will not be sent.
- **Treatment** – Subjects will self-administer treatment with the Elitone device or a sham device according to their group assignment. The prescribed number of treatments starts at 5x/week and is reduced at points throughout the 12-week study duration. See Section 6 and Table 5-1 for a detailed description of the device and the treatment schedule. If subjects are ill or in menses during the twelfth study week they are instructed to extend treatment for at least 5 days after menses and/or they are in good health.
- **Post-Study** – Upon completion of treatment subjects complete the post-study requirements, which include the I-QoL questionnaire, a 24-hour pad weight test, and a post-study usability

questionnaire. Subjects are requested to complete the requirements and return the study materials to Elidah within 3 days of completing treatment. There is no difference in post-study requirements between the two study arms.

Table 5-1: Schedule of Study Activities/Requirements for Active and Control Groups.

● - Data used in primary and secondary endpoint analysis ○ - Used to establish compliance.	I-QoL Questionnaire	24-Hour Pad Weight Test	Pre-Study Usability Questionnaire	Number of Self-administered Treatment	Daily Log	Post-Study Usability Questionnaire	Adverse Events
Pre-Study Data	●	●	●				
Baseline (Week 0)				0	●		
Treatment (Week 1)				5	○		●
Treatment (Week 2)				5	○		●
Treatment (Week 3)				5	○		●
Treatment (Week 4)				5	○		●
Treatment (Week 5)				5	○		●
Treatment (Week 6)				5	○		●
Treatment (Week 7)				3	○		●
Treatment (Week 8)				3	○		●
Treatment (Week 9)				3	○		●
Treatment (Week 10)				1	○		●
Treatment (Week 11)				1	○		●
Treatment (Week 12)				1	●		●
Treatment (Week 13)*				1	●		●
Post-Study Data	●	●				●	●
* As needed. See description of treatment above.							

5.5 Adherence Assessment

Adherence to the study regimen for the active group requires completion of ≥60% (18) of the treatment sessions prescribed during the first 6 weeks, as determined from review of each subject's Daily Log.

Elidah anticipates that subjects' willingness to continue with a frequent treatment schedule may diminish with time for reasons including:

- The subject achieves meaningful clinical improvement or complete elimination of incontinence symptoms during the early weeks of the study
- The subject believes she is in the control group
- The subject is not achieving clinical improvement and become discouraged with the likelihood of future improvement.

- Change in the subject's schedule and/or lifestyle

Accordingly, the prescribed treatment frequency over the latter half of the study is reduced (see Table 5-1). Correspondingly the minimum number of treatment sessions required for adherence is reduced to 1x/week for weeks 7-9 (33%) and 0x/week for weeks 10-12 (0%).

Further, subjects must complete the Pre-study, Baseline and Post-Study requirements to be considered compliant. If a subject does not adhere to the study requirements they will be asked to provide a reason, which will be documented in the Case Report Form (TR-1131-FORM-10). During data analysis, this information will be reviewed by the Data Safety and Monitoring Board to determine if/how the data should be adjudicated (see 10.5).

5.6 Concomitant Medications

Concomitant medications are defined as any prescription or over-the-counter medication (including hormonal contraception, vitamins, food supplements, and herbal preparations) taken seven days prior to initiation of pre-study activity through completion of post-study activity. Subjects will be instructed not to take any new concomitant medications unless medically necessary. If the use of a new concomitant medication becomes necessary, the treatment must be recorded in the Case Report Form (TR-1131-FORM-10), including the name of the medication, dosage, route of administration, date, and indication for use.

5.7 Blinding

Subjects will be blinded to the assigned treatment group. The individual(s) performing subject level data analysis will be blinded to the treatment arm. Due to the 2:1 assignment ratio blinding, assignment must be revealed during group analysis. See 9.3 for addition discussion of blinding.

6. ELITONE DEVICE

6.1 Device History

The Elitone device has been evaluated clinically in prior IRB approved study WIRB-20162650, WIRB 20180640. See 9.1 for additional information regarding the outcomes from that study. For the current study, only minor modifications have been implemented with respect to the software, stimulation waveform and treatment regimen.

6.2 Description of Treatment Regimen

The Elitone device delivers electrical current through an electrode component applied to the perineal region, stimulating the pelvic floor muscles and surrounding structures to improve continence. Per the product labeling, stimulation is delivered in continuous on-off cycles, 20 minutes per session, 5 sessions per week for 6-12 weeks. In this study, the treatment frequency is more explicitly defined as detailed in Table 5-1. The design allows for convenient home-use. It comprises two main components: a disposable electrode and a controller.

Figure 6-1: Rendering of Elitone device worn on the female anatomy, under clothing.

6.3 Electrode Component

The electrode component is worn against the skin in the perineal region. The conductive regions are positioned such that when stimulated they deliver electrical current proximate the pelvic floor muscles. The base of the electrode is a flexible conductive ink circuit. The patient contacting elements are hydrogel and foam. Two snap connections are present on the surface facing away from the patient, which provide a connection point to a cable and the Controller component. Each electrode is provided on a removable release liner that aids in maintaining the adhesiveness and hydration of the hydrogel during use and reuse. All materials used in the electrode have histories of use in similar electrodes.

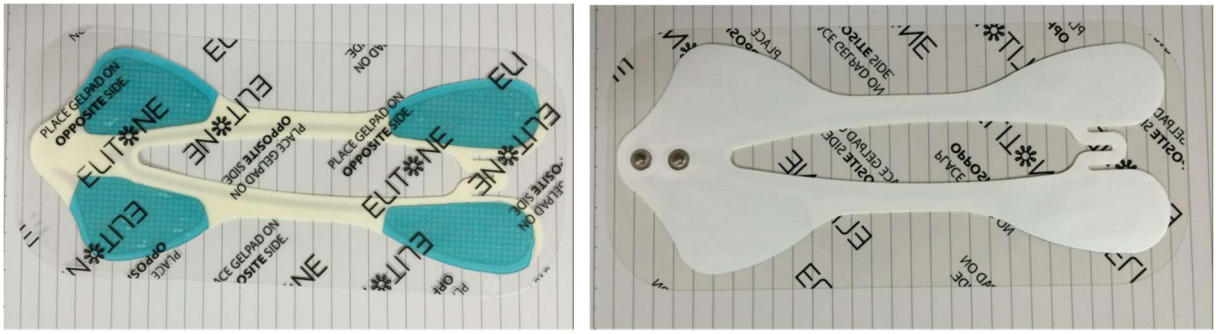

Figure 6-2: LEFT - Patient contacting side of electrode component, including conductive regions (blue) seen through the removable release liner. RIGHT - Opposite side of electrode component, including snaps for cable connection.

The electrodes are packaged in quantities of five in a resealable pouch. They are identified as part number EE-1002, and the packaging includes a lot number and Use By date. Each subject is provided with sufficient electrodes to allow use of a new electrode every other treatment session.

6.4 Controller Component and Accessories

The Controller component is used to supply the stimulating current. It comprises a circuit board, rechargeable battery, and user interface, all housed within a plastic housing approximately 2” x 1.5” x 0.5”. The device is programmed to deliver the stimulation waveform described in 6.5. The

device outputs 0-50mA (RMS) and 0-100V into a 500Ω load, which is similar to numerous commercially available electrical muscle stimulation devices and meets electrical safety standards for EMS devices (see 7.1). The output intensity is controlled by the user through a pair of increment and decrement buttons. The device can deliver at least two twenty-minute treatments on a battery charge. Recharging of the 3.7V lithium polymer battery is achieved via conventional micro-USB to USB cable. The battery includes integrated overload protection circuitry. In addition to the increment/decrement buttons, which also serve to turn on and pause/stop the device, the user interface includes a series of colored LEDs that indicate power state, and treatment intensity.

Each controller has a label that specifies the part number (EC-1003) and lot number. For the subject study, an additional label is applied that identifies the unit as "for investigational use only" and provides a unit reference number. Each subject is provided with a single controller. Accompanying the controller are additional components required for operation including the patient cable, USB charging cable, user manual, belt clip and product packaging. Note that portions of the user manual (TR-1131-FORM-12) have been modified to support blinding of the subject to her treatment group.

Figure 6-3: LEFT – Elitone controller. RIGHT – Controller and all accessories, including the User Manual, Patient Cable, Charging Cable, Belt-Clip (attached to Controller) and device packaging.

6.5 Stimulation Waveform

The Controller outputs a two part stimulation signal with a base of 2000 Hz and modulated at 50 Hz and 10 Hz. The first part operates at 50 Hz for 4 seconds and is intended to affect stress urinary incontinence symptoms. The second part operates at 10 Hz for 2 seconds and is intended to affect urge urinary incontinence. After the stimulation is delivered the output goes to zero for 6 seconds. This on/off cycling of the stimulation output continues for the duration of the treatment. Intensity is set by the user, who is instructed to operate the device at a level that is maximally tolerated for the duration of treatment. Variations on this stimulation signal are permissible and achievable due to circuit design, which utilizes a programmable microcontroller.

6.6 Control/Sham Device

Subjects in the control group will receive a sham device that is identical to the Elitone device except for the firmware parameters that define the stimulation waveform and therapy session.

The stimulation waveform for the sham occurs as a higher frequency and lower current, and the treatment session duration is also reduced. These parameters and intended to elicit a surface sensation, but not to induce contraction of the pelvic floor muscles or to have a therapeutic benefit.

As part of the post-study surveys subjects will be asked to describe any sensation they felt, whether they felt any contraction of the pelvic floor, and whether they believe they received a treatment or a sham device. The Data Safety and Monitoring Board will review the Case Repot Forms of any subjects in the control group who report contraction of the pelvic floor muscles (see 10.5)

6.7 Regulatory Status

The Elitone device is presently under review by the FDA as part of the De Novo process. This study is in part designed to support a request for additional information made by the FDA.

6.8 Procurement

The electrodes, controller and all accessories are designed and manufactured by Elidah, which operates in accordance with its ISO 13485 certification for the design and manufacture of medical devices. Where applicable the product will be provided to the subjects with suitable remaining shelf life. All subjects will receive new electrodes. Subjects may be provided previously used controllers or accessories that have been inspected and confirmed to meet performance requirements.

7. SAFETY ASSESSMENTS

7.1 Device Safety

Elidah believes that the Elitone device and the proposed protocol present low risk to the subjects. This assessment is supported by the following information:

- **Non-significant Risk Device Designation** - Electrical Neuromuscular Stimulators and Non-implantable Electrical Incontinence Devices have been designated as non-significant risk devices in FDA guidance document.[14] The Elitone device is represented by both of these product types and carries the same risk profile. The device is not life-sustaining and failure of the device to deliver its intended therapy does not result in any notable clinical consequence.
- **Developed within ISO 13485 Certified Quality Management System** – Elidah maintains ISO 13485 certification as a medical device manufacturer, meaning that development and production of the product adheres to accepted best practices for creating safe devices, including processes for continuous product and process improvement, reporting of complaints and adverse events, and quality control methodologies.
- **Independent Device Safety Testing** – The Elitone device has been tested by a third party laboratories and found to be compliant with the IEC-60601 family of standards (Medical Device Electrical Safety), including sub-standards specific to muscle stimulators and home use medical equipment. The device is also compliant with applicable IEC standards for electromagnetic compatibility.
- **Risk Mitigation by Design** – As part of the product development Elidah conducts design and process risk analyses intended to identify potential device safety concerns. The development team can then mitigate these concerns through design modifications and additional testing. Examples include:

  - Risks associated with electrical shock initiating from a supply main are mitigated by preventing device operation when the device is charging (i.e. connected to an external power supply) and by minimizing the length of the provided cables.
  - The device turns off automatically after 20 minutes.
  - A custom cable is used, which deters an individual from using one or more of the components with another device.
  - Output intensity is controlled by the user and is adjusted in ≤1mA increments, which limits the degree to which the user can be impacted by a "sudden" change in output intensity. Further, the circuit design limits the maximum current to approximately 50mA, a level consistent with commercially available EMS devices.
- **Risk Mitigation by Warnings/Precautions** – In cases where device safety concerns cannot be suitably mitigated by design, user instruction is provided in the form of warnings and precautions. The warnings/precautions provided in the Elitone User Manual TR-1131-FORM-12) have additionally been baselined against the product labeling for other electrical muscle stimulation devices used to treat incontinence, and aligned with FDA recommendations regarding product labeling. For example:
  - Users are instructed not to use the device while bathing.
  - Users are instructed not to wear the device while driving.
  - Users are instructed not to apply the device to the chest or eyes.
- **Alignment with Typical Therapeutic Use** – This study utilizes the device in a manner that is consistent with the devices performance characteristics and with traditional therapeutic use of electrical muscle stimulators. The selection of up to 20 minutes per day and 12 weeks of treatment (6.2) was intentionally selected as being consistent with the practice of physical therapy, so as not to run the risk of overly fatiguing the pelvic floor muscles.

7.2 Risks and Side Effects

Participation in the study will expose the subjects to risks and side effects similar to users of electrical muscle stimulators (EMS) and transcutaneous electrical nerve stimulation (TENS) devices, both of which are low risk devices as evidenced by multiple products cleared for over-the-counter use. Note that many of the warnings and precautions associated with general use EMS and TENS devices (e.g. don't place electrodes over the eye) are less applicable to Elitone due to the anatomic-specific nature of the Elitone device. However, as with most medical devices, use of the product does carry health risks and potential medical side effects. Elidah does not foresee any psychological, financial, or legal risks to the subject associated with participation in the study.

The User Manual (TR-1131-FORM-12) identifies applicable warning and precautions. Each candidate receives a copy of these warnings and precautions as part of providing informed consent (see 11.2). Broadly categorized, these risks and side effects include:

- **Electrical Shock** – The device delivers an electrical current to the body. Misuse of the device can result in an unintended shock which can be temporarily painful. Forms of misuse could include placing the electrode on another part of the body (e.g. across the chest) or turning the device on prior to applying the electrode to the body. The device, uses both hardware and software to control the output and has undergone extensive testing. As noted in 7.1, various safety measures are present to mitigate these risks.
- **Skin Irritation** – Although the materials used in the electrode are biocompatible and used in similar, commercially available electrodes, there is a risk of skin irritation. This is likely to be observed as persistent redness at the electrode application site, and is likely to resolve upon cessation of use.

- **Muscle Fatigue** – The treatment is intended to exercise the pelvic floor muscles, and the defined treatment regimen is guided by the recommended regimens of other EMS devices. However, some subject may experience notable muscle fatigue, which, in the near-term, could result in a temporary increase in urine leakage. Such occurrences are likely to resolve within a matter of hours.

7.3 Adverse Events and Serious Adverse Events

Adverse events are the primary means for assessing device/treatment safety. Adverse events may be identified through direct communication with the subjects and through analysis of study materials.

For all adverse events, sufficient information will be pursued and/or obtained so as to permit (1) an adequate determination of the outcome of the events (i.e., whether the effect should be classified as a serious adverse effect) and (2) an assessment of the casual relationship between the adverse event and the device/treatment.

Adverse events determined to be associated with the device/treatment will be followed until they are resolved or stabilized. The CTCAE definitions and scoring of Adverse Events will be used.

An **adverse event (AE)** is generally defined as any unfavorable and unintended symptom or finding which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen during the study. Adverse events are recorded regardless of their relationship to the study intervention.
A **serious adverse event (SAE)** is generally defined as any adverse event that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly: Grades 3-5.

7.4 Reporting Procedures

Subjects are instructed to report adverse events at the time of occurrence via either phone or email. Adverse events may also be identified during routine communication with the subject (e.g. 6th week follow-up) or review of the subject's Daily Log.

The Data Safety and Monitoring Board will use the following 0 to 5 scale to grade adverse events (AE): 0 = none or event is not clinically significant, 1 = mild AE that does not require treatment, 2 = moderate AE that does require treatment, but resolves completely, 3 = severe AE (e.g. one that results in temporary inability to conduct one or more everyday activities and requires ongoing medical attention), 4 = life threatening or results in permanent inability to conduct one or more everyday activities, and 5 = death.

In the event of an AE rated ≥2 the Clinical Director will instruct the subject to obtain medical treatment from a qualified healthcare professional. If the subject becomes ill or is physically injured due to the use of the Elitone™ device, she will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by the study device or properly performed non-standard of care investigational procedure required by the study will be covered by Elidah, as long as the subject has followed the study protocol. The subject will not lose any of her legal rights and she does not release Elidah and the study staff from liability for mistakes or intentional misconduct by participating in the study.

7.5 Follow-up for Adverse Events

The Clinical Director will follow up all AE rated ≥2 until they are resolved/stable. The Clinical Director will follow procedures of the CAPA system to address the events.

8. INTERVENTION DISCONTINUATION

Subjects in the study have the right to discontinue treatment at any point during the study and for any reason. If the subject chooses to discontinue, a reason for discontinuation will be recorded and every effort will be made for the subject to complete the post-study activities defined in Table 5-1.

Elidah may wish to discontinue intervention for a subject for a variety of reasons including those listed below. Effort will be made to bring the subject into study compliance prior to terminating participation.

- Purposeful improper use of the device
- Failure to treat per the assigned schedule
- A recurring adverse event or unanticipated problem.
- Failure to maintain the Daily Log for greater than 2 weeks

A pause on enrollment and/or treatment of active subjects may occur if Elidah discovers a serious issue with the device/treatment (see 7.3). Elidah maintains the right to discontinue the study at any point and for any reason. Stopping treatment does not pose any risk to subjects. The study may be discontinued at any time by the IRB, FDA, or other regulatory or government agency as part of their duties to ensure that research participants are protected.

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size and Power Analysis

The study is designed to test the null hypothesis that the treatment group and control group are not different (see 2.3). Specific reference is made to the number of subjects who achieve a ≥50% reduction in stress urinary incontinence episodes per day when comparing the final outcome to a baseline measure. Several comparable studies were identified in the literature in which similar "≥50% reduction in episodes" metrics were reported. From these, sample-size calculations were performed to provide confidence that sufficient subjects would be enrolled to protect against Type II error. Each of these calculations target 80% power and assume an alpha of 2.5%, a 2:1 treatment to control randomization ratio, and a single-tailed test.

- From Sand *et al*[1], 48% of subjects in the active group (2 treatments per day) were responders compared to 13% of subjects in a control (sham) group. Using these values in a chi-squared sample size calculation one finds that the treatment group for the proposed study needs to enroll 31 subjects.

[1] Sand et al, "Pelvic floor electrical stimulation in the treatment of genuine stress incontinence: A multi-center, placebo-controlled trial", Am J Obstet Cycecol, 173(1):72-79, July 1995.

- From Richardson *et al*[2], 62% and 73% of subjects (1 treatment/day and 1 treatment every other day) were responders. This study makes reference to the response rate for the sham group in the Sand et al study (13%). Using the 62% and 13% values in a chi-squared sample size calculation one finds that the treatment group for the proposed study should include 16 subjects.
- From a similar, ongoing study in which Elidah is also the Investigator (WIRB-20162650), to date, 71% of subjects are responders. Conservatively estimating the control responder rate at 15% (about the average rate reported in the AHRQ meta-analysis for the control groups in studies using vaginal EMS, Table F97), using a chi-squared sample size calculation one finds that the treatment group for the proposed study needs to enroll 12 subjects.

These three analyses suggest a treatment group in the range of 12-31 subjects. Taking a conservative approach, Elidah will aim to enroll 40 subjects in the treatment group and 20 subjects in the control group. At that level of enrollment, responder rates of 60% and 25% would give p=0.01. Anticipating that some subjects will drop out throughout the study, a total of 70-80 subjects will be identified for participation. See 9.4 regarding interim analysis and stopping rules.

9.2 Randomization

A subject is assigned to the active or control group upon returning her informed consent documentation. Assignment is based on pre-set randomization of small groupings. For example, a card drawn from a deck of nine cards, wherein each card is indicated as either active or control according to a 2:1 ratio (i.e. 6 cards are identified as active and 3 card as control). After a card has been drawn it is removed from the deck. After the ninth subject is assigned to the group corresponding to the ninth card, the nine card deck is re-shuffled and a card is drawn for the tenth subject. This process continues until enrollment is complete. Means equivalent to a card draw may alternately be used.

9.3 Blinding

Subjects will be blinded to their treatment group. As described in 6.6, with the exception of the firmware loaded on the Controller component, the devices used in the active and control groups are identical, so visualization and handling of the device by the subject will not compromise the blinding. The devices in both groups generate an electrical output that is perceived by the subject, which reduces the risk of subjects identifying themselves as in the control group. The device user manual (TR-1131-FORM-12) and subject instructions (TR-1131-FORM-15) have been modified/written to eliminate language that might suggest to a subject that she is one group or the other. Similarly, study personnel will be instructed to avoid use of language that might indicate which group a subject is enrolled.

Randomization as defined in 9.2 is implemented by an individual who does not interact with the subjects. Study staff who interact with the subjects are blinded to the randomization. Note however, that there is a risk that study staff who interact with the subjects may be informed of group assignment based on comments by the subjects during the study (e.g. if the subject

[2] Richardson et al, "Pelvic floor electrical stimulation: A comparison of daily and every-other-day therapy for genuine stress incontinence", Adult Urology, 48(1):110-118, 1996.

describes the stimulation in a way that makes the stimulation identifiable). Such comments would be documented in the subject's Case Report File. This unblinding would have little impact on data integrity as the study personnel is not involved in the reporting of outcome measures.

Study personnel who analyze individual subject data will be blinded to group assignment. For example, baseline and 12th week episodes/day calculations and pad weight measurements will be made for each subject by blinded study personnel. Later, when group analysis is performed, blinding will be necessarily broken due to the unequal enrollment ratio.

9.4 Interim Analyses and Stopping Rules

The study will include an interim analyses after 30 and 45 subjects have completed enrollment. The Hyabittle-Peto method will be used determine whether the study should be stopped due to extreme differences between the active and control groups. At either interim analysis if the p-value for the primary efficacy outcome is <0.0013 the study will be determined to have met the endpoint.

In the event of a serious adverse event related to the device/treatment the study will be halted until the safety issue can be addressed (see 7). Due to the small enrollment size, a pre-specified number of adverse events will not be used to trigger an interim analysis or early end to the study.

9.5 Data Analyses

Analysis of the **primary efficacy endpoint** will proceed as follows. Each adherent subject's Daily Log will be used to determine the average number of SUI episodes per day for the baseline and 12th weeks (see 5.5 regarding subject adherence). To accommodate the likelihood that some subjects will omit log data, the "weeks" referred to in the baseline and 12th week assessments refer to the first and last 5 entries in the Daily Log. The percent reduction in SUI episodes is then calculated by subtracting the final week average from the baseline average, dividing the difference by the baseline average, and multiplying by 100. Subjects with a percent reduction of ≥50% are considered responders. The number of responders from each group is then compared using a one-tailed Fisher's exact test for groups of unequal size, and p≤0.025. For example, if 24 of 40 subjects (60%) from the active group responded and 5 of 20 (25%) from the control group responded, the active treatment would be considered effective (p=0.01).

SUI episodes per day data can additionally be characterized simply in terms of percent reduction (independent of whether it reaches a 50% level of clinical significance) and the treatment groups analyzed using a 2 sample t-test with unequal group sizes. This approach is commonly reported in the literature. This value may additionally be reported but is not intended for use in determining whether the study met its endpoint. This use of a secondary analysis method on a single endpoint after success of the primary analysis method is generally understood to not inflate the Type 1 error rate, so no multiplicity adjustments are necessary.

Also note that confidence intervals and associated effect size calculations may also be made on the same data, but no multiplicity adjustments are warranted. Similarly, the data may be additionally analyzed using intent-to-treat criteria instead of with per-protocol criteria as defined in 5.5.

Regarding **secondary outcome measures**, three tests are prospectively defined with the intent of using the results to support future product labeling and marketing. The Hochberg procedure

with a total alpha of 0.05 will be used to address multiple endpoint related multiplicity problems. These secondary outcome measures are only intended to be analyzed if the primary efficacy endpoint is met. Accordingly, no Type 1 error rate multiplicity adjustment is retrospectively applied to the primary endpoint. The three test are:

- **24h Pad Weight** – Subjects with pad weight reductions of ≥50% (i.e. clinically significant) will be considered responders and the groups will be compared using the Fisher's exact test in a similar manner to the analysis of the primary outcome measure.
- **I-QoL** – Quality of life scores will be analyzed with respect to a change from baseline. Responders will be those with an I-QoL score increase of 2.5 points, which is defined in the FDA guidance as clinically significant. Treatment and control groups will be compared using the Fisher's exact test.
- **Pad Use** - As with the 24h pad weight test, reduction in pad usage will be assessed with respect to a reduction in the number of pads used per day and a 50% reduction will be considered clinically significant. Subjects who do not use a pad during the baseline week will be excluded from the analysis.

Other analyses that may be made but which are not prospectively included within the group of three formal secondary outcome measures (and therefore are not considered with respect to multiplicity adjustments) include:

- Alternate analysis methods for the 24h Pad Weight, I-QoL and Pad Use test will be performed. For each, the mass/score/number data can analyzed using a paired sample t-test to determine whether there is a mean difference between the groups. Further, for the 24h Pad Weight test, a "cure" rate may also be calculated wherein a cure is defined in terms of dryness, which the FDA guidance document recommends defining as a pad weight increase of less than 1.3 grams.
- Usability surveys will solicit subject feedback pertaining to their experience with the product. Appropriate statistical methods will be used in reporting these subjective measures. For example, the Fisher's exact test may be used to determine whether a significant difference exists in responses to the question "Are you satisfied with the treatment"

In addition to characterizing outcome measures as achieving a clinically meaningful response (e.g. ≥50% change) or as change scores (i.e. delta values), post hoc analyses may investigate outcome measures using analysis of covariance (ANCOVA), wherein baseline values are modeled as covariates, which has the advantage of accounting for variation in the magnitude of the baseline. Additional post hoc ANCOVA may be performed with covariates including age, type of incontinence, BMI or other potentially relevant variables.

9.6 Data Pooling

This study is, in part, being conducted to provide scientific evidence to support FDA clearance of the Elitone device. Accordingly, the FDA has provided input regarding aspects of the study design including the outcome measures and the sample size. As part of the regulatory review process, Elidah is considering augmenting data from this study with data from other studies. This approach may enable pooling of data from the multiple studies, which may reduce the number of required subjects in this study. If it is determined that fewer subject are necessary, Elidah may opt to terminate this study or alter the group assignment ratio. If this occurs, enrolled subjects will complete the full course of treatment.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Subjects will provide data using the following forms:

- Pre-Study Questionnaire (TR-1131-FORM-1)
- I-QoL Questionnaire (TR-1131-FORM-2)
- Daily Log (TR-1131-FORM-3)
- Post-Study Questionnaire (TR-1131-FORM-3)

The forms are sent to the subjects in hardcopy and subjects return the completed forms to Elidah in envelopes with pre-paid postage. Returned forms are identified by the subject's ID Number and stored in the corresponding subject folder in the study binders. Electronic equivalents may also be utilized.

10.2 Materials Management

In addition to the items described in 10.1, at the beginning of the study each subject will receive the following:

- Elitone controller and accessories (see 6.4)
- Elitone electrodes (see 6.3)
- User Manual (TR-1131-FORM-12)
- Absorbent pads
- Leak-proof specimen bags
- Pre-paid postage and packaging

Upon completion of the study, subjects in the active group are required to return the controller, accessories and any unused electrodes. Elidah will reconcile these components on the Case Report Form (TR-1131-FORM-10).

10.3 Specimen Management

As part of the 24-hour pad weight tests, used absorbent pads will be mailed to Elidah to be weighed. Elidah will use universal precautions during receipt, inspection (i.e. weighing) and disposal of the specimens. Specimens will not be retained after they are weighed.

10.4 Data Management

All subject folders and study binders will be kept in a locked cabinet at Elidah.

Data from the forms will be transferred to electronic formats (e.g. Excel) for analysis, but only in formats that do not include identifying subject data. This data may be generally accessible to Elidah staff and included in formal test reports within Elidah's Quality Management System.

Subject identifying data may be converted to an electronic format, but will not be generally accessible to Elidah staff.

In accordance with HIPPA requirements, at the conclusion of the study all study binders (or equivalent electronic files) will be maintained under lock and key for a minimum of seven years after last patient participation.

10.5 Data and Safety Monitoring Plan

Elidah will identify a Clinical Director who will be responsible for managing the study and ensuring that the rights and well-being of human subjects are protected, that the reported data are accurate and complete and verifiable from source documents, and that the conduct of the trial is in compliance with the approved protocol, with good clinical practice, and with applicable regulatory requirements. Specific responsibilities of the Clinical Director include:

- Verify that equipment and staff are adequate to safely and properly conduct the study
- Verify that subjects:
  - Meet eligibility requirements
  - Provided informed consent prior to enrollment
  - Are adequately informed about the device use, study requirements and risks of participation
  - Receive all necessary study materials
  - Return all the required data collection forms and specimens
- Verify that, with respect to the device:
  - That shelf-life and storage conditions meet requirements (as applicable)
  - Sufficient supplies (i.e. electrodes, controllers) are sufficient to complete the study
  - That the device is provided only to eligible subjects
  - That the receipt, use, and return of the device is controlled and complies with applicable regulation.
- Verify that source documents and data analyses are accurate and complete
- Verify that adverse events are appropriately reported
- Verify that protocol deviations are appropriately reported

In addition, a Data Safety and Monitoring Board will be established which will review study compliance and adverse events. The Data Safety and Monitoring Board will comprise, at a minimum, the Clinical Director, an individual responsible for technological aspects of the device and an individual with medical training relevant to the used of the device.

Currently, EMS and TENS devices are sold over the counter and used in an at-home environment. Given the high degree of similarity between those devices and the Elitone device, the described level of monitoring is considered appropriate for the low level of risk (see 7).

10.6 Quality Assurance

- **Training** –The Clinical Director is responsible for ensuring that the study staff can perform the responsibilities they have been assigned. All study staff will be required to complete the NIH Protection of Human Subjects Training before performing any function of the study.
- **Quality Control Committee** – Given to the small scope of the study, a Quality Control Committee will not be utilized. The Clinical Director has responsibility pertaining to maintenance of study quality, and the Data Safety and Monitoring Board exists to ensure appropriate human protection regulations are met and adverse events are appropriately handled.
- **Metrics** – Section 9.5 defines that data analysis and statistical approach used to determine study success. Upon completion of the analysis one or more persons not

involved with the original data analysis will audit the data entry, mathematical calculations and statistically driven conclusions.

- **Protocol Deviations** – Protocol deviations will be documented using Protocol Deviation Log (TR-1131-FORM-8) and retained within the Study Binders. The Clinical Director and/or Data Safety and Monitoring Board will make the determination of whether the impact of the deviation should be considered in subsequent analysis.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol, including the informed consent document (see 11.2), and any subsequent modifications will be reviewed and approved by the IRB.

11.2 Informed Consent Form

TR-1131-FORM-5 includes information intended to allow the candidate to make the decision to provide informed consent, including descriptions of the protocol, participant requirements and potential risks. Among other requirements (see 4.1 and 4.2), individuals not allowed to participate in the study include:

- Minors
- Individuals who do not speak and read English
- Individuals who are unable to consent for themselves

Upon receiving the informed consent documentation the candidate may ask questions and take the necessary time required to read and comprehend the information. If the subject agrees to provide informed consent, she will sign an informed consent document. A copy is provided to the subject. Elidah's copy of the signed document is maintained in the Subject Folder. The consent may be an e-consent format.

11.3 Participant Confidentiality

During the screening process (see 4.3) each candidate will be assigned a screening number. The subject's name and identifying data such as contact information will be stored in the Screening Log (TR-1131-FORM-11), which is maintained within the study binders (see 10.4).

One the subject is enrolled, her name is entered into the Enrollment Log (TR-1131-FORM-6). This is the only document that links the assigned Subject Number to a subject's name and contact information. The Enrollment Log is maintained within the study binders (10.4). All communication among study staff utilizes the Subject Number.

Identifying information will not be released without written permission of the subject except as required by the IRB, FDA or other regulatory body. In the event of written publication, results will be disclosed reflecting group statistics or without identifying information in order to protect subject confidentiality.

11. APPENDICES

(As separate documents)

- TR-1131-FORM-1 – Pre-Study Questionnaire

- TR-1131-FORM-2 – I-QoL Questionnaire
- TR-1131-FORM-3 – Daily Log
- TR-1131-FORM-4 – Post-Study Questionnaire
- TR-1131-FORM-5 – Informed Consent Form
- TR-1131-FORM-6 – Enrollment Log
- TR-1131-FORM-7 – Subject Code Log
- TR-1131-FORM-8 – Protocol Deviation Log
- TR-1131-FORM-9 – Adverse Event Log
- TR-1131-FORM-10 – Case Report File
- TR-1131-FORM-11 – Screening Log
- TR-1131-FORM-12 – User Manual
- TR-1131-FORM-13 – Screening Questions
- TR-1131-FORM-14 – Candidate Recruitment Language
- TR-1131-FORM-15 – Subject Instructions

REFERENCES

[1] Nitti, VW, "The prevalence of urinary incontinence", Rev Urol. 2001; 3(suppl1):S2-S6.

[2] Milsom I, "Lower urinary tract symptoms in women".Curr Opin Urol 2009, 19(4):337-41.

[3] Minassian V, Drutz H, Al-Badr A, "Urinary incontinence as a worldwide problem", Int J Obstet Gynecol 2002, 82:327-338.

[4] Sahin-Onat, Sule et al., "Relationship between urinary incontinence and quality of life/depression in elderly patients," Journal of Clinical Gerontology and Geriatrics, Volume 5 , Issue 3 , pp 86 – 90.

[5] Bø K, Kvarstein B, Nygaard I: Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 105:999-1005, 2005.

[6] "Decision Memo for Pelvic Floor Electrical Stimulation for Urinary Incontinence (CAG-0021N). Centers for Medicare & Medicaid Services (2000). https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?&NCAId=61&#1@bc=AAAAAAAAAAAQAA==@&from=https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=61@fromdb=true (accessed December 22, 2015).

[7] Hampel C., Weinhold D., Benken N., "Definition of overactive bladder and epidemiology of urinary incontinence". Urology 1997; 50: 4-14.

[8] Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: AUA/SUFU Guideline AUA/SUFU Guideline: Published 2012; Amended 2014.

[9] Kondo A, Emoto A, Katoh K, et al: Long-term results of the pelvic floor muscle training for female urinary incontinence: an 8-year transition tree and predictive parameters. Neurourol Urodyn 26:495-501, 2007.

[10] Interviews by Gloria Kolb with more than a 50 urologists and gynecologists and 160 women and patients. Unpublished, 2014-2016.

[11] Dumoulin, C, Hay-Smith EJC, Mac Habee-Seguin G, "Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women (Review)", Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD005654. DOI:10.1002/14651858.CD005654.pub3.

[12] "Women's Health: U.S. Markets for Female Urinary Incontinence Therapies." February 2014. MedTech Insight web site. http://www.medtechinsight.com/ReportA472.html. (Accessed March 12, 2014).

[13] Correia, CN; Pereira, VS; Hirakawa, HS; Driusso, P; "Effects of surface intravaginal electrical stimulation in the treatment of women with stress urinary incontinence: randomized controlled trial", Eur J Obstet Gynecol 2013.

[14] Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies. FDA, CDRH. 2006. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

[15] FDA Guidance Document, "Clinical investigations of devices indicated for the treatment of urinary incontinence", March 8, 2011.

[16] R. O'Sullivan, E. Karantanis, T.L. Stevermuer, et al. Definition of mild, moderate and severe incontinence on the 24-hour pad test. BJOG: an International Journal of Obstetrics and Gynaecology. August 2004, Vol. 111, pp. 859–862.