Clinical Study to Evaluate the Efficacy of Surface Electrical Stimulation for Urge 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): Electrical muscle stimulators and electrodes are designated by FDA as non-significant risk devices. No IDE required.

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1. EXECUTIVE SUMMARY.

1.1 Study Title

Clinical Study to Evaluate the Efficacy of Surface Electrical Stimulation for Urge Urinary Incontinence in Women.

1.2 Objectives

The primary objective is to demonstrate the safety and efficacy of the ELITONE-UUI device for urge urinary incontinence.

1.3 Design and Outcomes

This is a case series with two treatment groups. Pre- and post-study outcome measures evaluate the change in incontinence episodes (i.e. leaks), leaks, bathroom visits, and quality of life.

1.4 Interventions and Duration

Participants will self-administer electrical stimulation using the ELITONE-UUI device, 20-25 minutes per session, 4-5x per week, for 6 weeks. Participants will be randomly assigned to one of two groups, each group receiving a different device configuration wherein the stimulation frequency (e.g. 10Hz, 50Hz) differs between the groups. The ELTIONE-UUI device is identical to Elidah's ELITONE device, except for the digitally controlled stimulation parameters.

1.5 Sample Size and Population

The population includes women ages 21-80 with mild-moderate urge urinary incontinence or mild-moderate mixed urinary incontinence with predominant urge symptoms. The study intends to have 20 women complete the study in each group.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

The primary objective of this study is to demonstrate the safety and efficacy ELITONE-UUI device as a conservative treatment for urge urinary incontinence.

2.2 Primary Endpoint

Treatment efficacy is assessed by comparing the average number of 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

This case series is not a hypothesis driven study. The expectation is that both treatment groups will realize a clinically meaningful reduction (≥50%) in urinary incontinence episodes per day

relative to a pre-treatment baseline. Secondary measures may also show clinically meaningful changes. Differences between the groups may inform selection of a device configuration to move toward product commercialization.

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. 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.

- Incontinence Quality of Life score (I-QoL)
- Pads per Day
- Urge Incontinence Episodes without a Leak
- Urge Incontinence Episodes with a Leak
- Bathroom Visits per Day
- Nighttime Bathroom Visits
- Usability Data (e.g. Ease of Use, Satisfaction, Preferred Intensity Settings)
- Treatment Compliance

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. Often women do not want the medication that is available for Urge Urinary Incontinence (UUI) due to potential interference with other medications. There are implantable and percutaneous electrical stimulation devices, which can provide relief although can be expensive or require weekly office visits.

Electrical muscle stimulation (EMS) of the pelvic floor muscles and surrounding structures has proven effective in treating UUI and multiple "e-stim" devices have received FDA clearance to treat UUI (e.g. Intone, Kegel8, Yarlap). However, these devices deliver the stimulation via an intravaginal probe. Women often find this method uncomfortable. Further, these intravaginal devices necessitate a private location and dedicated treatment time (often at a treatment center), which challenges the likelihood of adoption.[5,6,7]

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.[6] This

leads to two thirds of affected women suffering quietly without treatment while conditions worsen.[8] Thus, the need exists for a non-invasive means of treating UUI that has a higher rate of patient adoption and compliance than current solutions.

3.2 Study Rationale

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).*[9]

There is a long history of use of intravaginal EMS for treatment of SUI and UUI, and it is predicated on the assumption that proximity of the electrodes to the pelvic floor and bladder 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 devices offset any benefit from the treatment's intimate electrode placement.

Clinical reports have suggested that a pattern of surface electrodes placed in the suprapubic and ischial tuberosity regions are as effective as intravaginal electrodes at treating SUI and UUI.[10,11,12,13] 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 developed a wearable, use-at-home SUI specific muscle stimulation device called ELITONE. Elidah has conducted clinical trials of ELITONE (WIRB 20162650, WIRB 20180640) and observed clinically meaningful improvements in SUI symptoms without serious adverse events. For example, the subjects reported an average reduction in leaks of 72%, and 75% of subjects had a clinically significant (≥50%) reduction in leaks. That device received FDA clearance as an SUI treatment in 2019.

Elidah now seeks to evaluate an alternate device configurations of the ELITONE device in which the output has been changed to a frequency understood to more directly affect UUI symptoms. Throughout this protocol the UUI device configurations are referred to as ELITONE-UUI.

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-1155-FORM-10).

- Predominant urge urinary incontinence as determined by responses to a series of three standard questions from the King's Health Questionnaire; specifically:
    - An affirmative response to "Is it very difficult to control when you have a strong urge to urinate?",

    - An affirmative or negative response to "Do you lose urine with physical activities such as coughing, sneezing, running?",
    - And, if an affirmative response to the second question, an affirmative 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 or more per 24 hours. Symptom severity is later verified with data from the Daily Log (See 5.4)
- Age: 21-80y
- Gender: Female

4.2 Exclusion Criteria.

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

- Less than 1 incontinence accident (leak) per day*
- Severe incontinence as determined by self-reported >5 accidents per day
- Currently pregnant, may be pregnant, attempting to become pregnant, or delivery within previous 6 weeks
- Vaginal or pelvic surgery within previous 6 months
- Severe Obesity as defined by BMI >= 35
- Change in incontinence medication type or dosing within the last 3 months.
- History or symptoms of urinary retention, extra-urethral incontinence, overflow incontinence
- Pelvic pain/painful bladder syndrome
- Active urinary tract infection (UTI) or history of recurrent UTIs (more than three in a year), or recurrent vaginitis (bacterial/fungal)
- Tissues protruding outside the vagina at rest
- Presence of incontinence-associated dermatitis or other perineal skin disorders or lesions,
- Complete denervation of the pelvic floor
- Conductive inter-uterine devise (IUD/Coil) or metal implants in the abdominal or pelvic area, including the hip and lumbar spine,
- Chronic coughing
- Previous use of Interstim device or Botox for UI
- Implanted cardiac device, untreated cardiac arrhythmia or suffer from other heart problems.
- Cancer, epilepsy or cognitive dysfunction
- Underlying neurologic/neuromuscular disorder
- Impaired decision making, suicidal thoughts, or drug/alcohol dependence
- Lacks capacity to consent for themselves.

* During the baseline week subjects will be excluded if they average less than 1 urge incontinence episode per day (with or without a leak).

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 to attract candidates to a website that describes the study. These ads will be places in the US without regional geographic targeting and use key words including “incontinence” and “bladder leaks”
- Email to a list of women with urge incontinence who had previously expressed interest in participating in a clinical study.
- 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 to Elidah.
- TR-1155-FORM-14 identifies the language that will be used in recruitment messaging.

Screening

- Interested candidates complete an online survey comprising Screening Questions (TR-1155-FORM-13)
- Responses are maintained electronically in a Screening Log (TR-1155-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-1155-FORM-10) if enrolled, or in the screening log if not enrolled.
- Consent documentation (TR-1155-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-1155-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 (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, 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.

- Subjects will have access to the ELITONE-UUI device for $100 deposit, which is a substantial discount compared to the commercially available ELITONE device which retails for $399.

4.5 Retention Strategies

- Subjects who complete the study will receive their deposit back. If the subject does not complete all study requirements the Clinical Director has discretion to compensate with a lesser amount.
- Subjects will be informed that the device records usage/compliance.
- Bi-weekly monitoring of digital treatment diary by study staff, with email/phone follow-up as needed.

5. STUDY DESIGN & PROCEDURES

5.1 Study Type

Case series with two treatment groups.

5.2 Number of Subjects

20 subjects per treatment group (40 total). Appreciating that some subjects who are initially enrolled will fail to complete treatment and return the study materials, it is likely that 50-55 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.[14] 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-1155-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.[14] 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).
- **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-1155-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 6th 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-1155-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 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-1155-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 and the Pre-study Incontinence History. The subject submits the pre-study materials to Elidah (electronically or hardcopy).
- **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.
- **Verification** - If the 7 day Baseline shows that the subject does not qualify based on urinary incontinence episode exclusion criteria (<1/day, >5/day) then the subject will be disqualified and the device will not be sent. The subject will be notified of disqualification, or if qualified, will be sent a link for deposit payment/hold. Qualifying subjects will be randomly assigned to a treatment group and a corresponding ELITONE-UUI device will be mailed to them.
- **Treatment** – Subjects will self-administer treatment with the ELITONE-UUI device. Subjects will treat 5x/week for six weeks. Each treatment is 20 minutes. No more than one treatment per day. See Section 6 and Table 5-1 for a detailed description of the device and treatment regimen. If subjects are ill or in menses during the 6th study week they are instructed to extend treatment for at least 5 days after menses and/or they are in good health. During the treatment weeks subjects are required to maintain their Daily Log. There is no difference in treatment requirements between the two treatment groups.
- **Post-Study** – Upon completion of treatment subjects complete the post-study requirements, which include the I-QoL questionnaire 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 treatment groups.

Table 5-1: Schedule of Subject Activities/Requirements.

● - Data used in primary and secondary endpoint analysis ○ - Used to establish compliance.	I-QoL Questionnaire	Pre-Study 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)*			5	●		●
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 ≥20 of the 30 prescribed treatment sessions, as determined from review of each subject's Daily Log and the device's memory.

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-1155-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-1155-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 treatment group. Study staff will not be blinded to the treatment group. This is done to enable staff to respond to questions regarding the timing (i.e. on/off cycles) of the stimulation, which is treatment group specific. 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 studies (WIRB-20162650, WIRB 20180640). See 9.1 for additional information regarding the outcomes from those studies. The product was FDA cleared in 2019 for OTC use and is commercially available. For the current study, minor software modifications have been implemented that affect the stimulation waveform and treatment regimen. In this protocol the modified configurations are referred to as ELITONE-UUI.

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, 4-5 sessions per week for 6-12 weeks. For this protocol, the treatment 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.

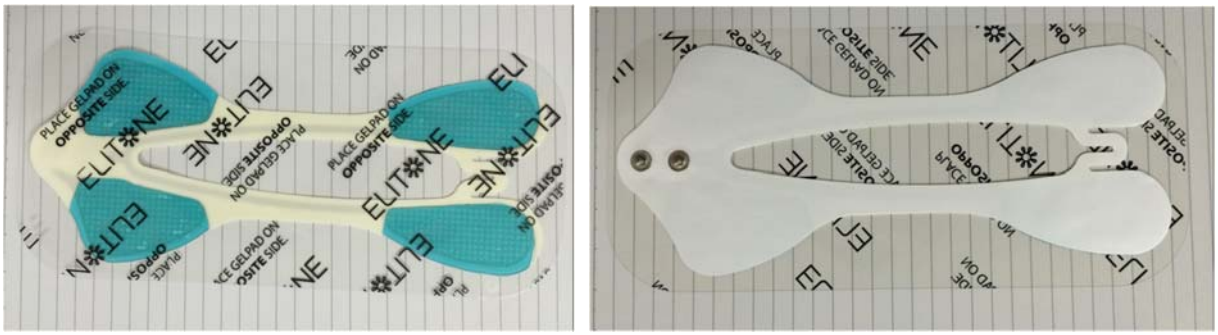

Figure 6-2: LEFT - Patient contacting side of electrode component, including conductive regions (blue) seen through the removable release liner. RIGHT - Opposite side of electrode component, including snaps for cable connection.

The electrodes are packaged in quantities of five in a resealable pouch. They are identified as part number EE-1011, 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-1155-FORM-12) have been modified to support blinding of the subject to her treatment group.

Figure 6-3: ELITONE 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 ELITONE device outputs a two part stimulation signal, delivered at 50 Hz and 10 Hz, both modulated at 2000 Hz. The first (50 Hz) part runs for 4 seconds and the second part (10 Hz) runs for 2 seconds. It is generally understood that a 50 Hz stimulation treats SUI and a 10 Hz frequency treats UUI. After these 6 seconds of stimulation the output goes to zero for 6 additional seconds. This on/off cycling of the stimulation 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, but not painful, for the duration of treatment.

The ELITONE-UUI device increases the proportion of the signal that operates at 10 Hz, intending to have a more substantial effect on UUI symptoms. Configurations are as follows:

- **Configuration 1** – 4 seconds at 50 Hz, followed by 4 seconds at 10 Hz, followed by 6 seconds of rest, repeated.
- **Configuration 2** – 6 seconds at 10 Hz followed by 6 seconds of rest, repeated. No 50 Hz stimulation is provided in this variant.

These configurations are achievable solely through software changes.

Should one or both configurations be determined to have minimal effect on the UUI, up to two additional configurations may be considered for clinical evaluation. These additional configurations include:

- **Additional Configuration 3** – 4 seconds at 50 Hz, followed by 4 seconds at 10 Hz, followed by 6 seconds of rest, repeated for 10 minutes. Then, 6 seconds at 10 Hz followed by 6 seconds of rest, repeated for 10 minutes.
- **Additional Configuration 4** – Current ELITONE stimulation as defined above.

6.6 Control/Sham Device

There is no control/sham group in this study

6.7 Regulatory Status

The ELITONE device received FDA clearance for OTC use in the treatment of female stress urinary incontinence. This study is in part designed to generate clinical data likely necessary to support FDA clearance of the proposed ELITONE-UUI device.

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. 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. The ELITONE-UUI product is identical to the commercially available ELITONE device with the exception of the embedded software, which will be programmed and verified by Elidah prior to shipment of product to the subjects.

7. SAFETY ASSESSMENTS

7.1 Device Safety

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

- **Equivalence to the ELITONE Device** – The only difference between the ELITONE-UUI device and the FDA cleared, commercially available ELITONE device is the embedded software that defines the stimulation waveform.
- **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.[9] The ELITONE-UUI 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 User Manual TR-1155-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 6 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-UUI due to the anatomic-specific nature of the ELITONE-UUI 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-1155-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 causal 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 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-UUI 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 1 week

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 proposed case series study design is not hypothesis driven (see 2.3). It is designed to parallel the prior 20-subject ELITONE case series that investigated use in treating SUI and that was presented to FDA in support of 510(k) clearance. That study showed a 72% reduction in daily leaks and a 75% responder rate. Elidah anticipates that a ≥50% reduction in leaks/day and/or a ≥50% leaks/day responder rate will be adequate to support FDA clearance of the ELITONE-UUI device.

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 achieve a measurable result.

- 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 an RCT study needs to enroll 31 subjects.

[1] Sand et al, "Pelvic floor electrical stimulation in the treatment of genuine urge 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 an RCT 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 an RCT study needs to enroll 12 subjects.

These three analyses suggest a treatment group in the range of 12-31 subjects would be suitable for an RCT study. Taking a conservative approach, and appreciating that the proposed study is not an RCT design, Elidah will aim to enroll 20 subjects in each treatment group, for a total of 40 subjects. See 9.4 regarding interim analysis and stopping rules.

9.2 Randomization

Subjects are assigned to a treatment group at the time the device is shipped to the subject. Assignments are made alternating between Group 1 and 2 until enrollment is complete.

9.3 Blinding

The instructional materials provided to each subject will include a brief description of the waveform (e.g. 4 seconds with one stimulation, followed by 4 seconds of a slightly different stimulation, followed by 6 seconds of rest), which aides is establishing expectations of proper function and identification of a suitable treatment intensity. Accordingly, the subjects and staff members interacting with those subjects are not considered to be blinded.

Study personnel responsible for post-treatment data analysis will be blinded from the group assignment during analysis of individual subject data. For example, baseline and 6th week episodes/day calculations and pad weight measurements will be made for each subject without knowledge of group assignment.

9.4 Interim Analyses and Stopping Rules

Due to the short duration of the study (6 weeks) and likely rapid enrollment (1 month), there are no plans for an interim analysis.

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 early end to the study.

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

9.5 Data Analyses

This is not a hypothesis driven study. Descriptive statistics will be the primary means of data analysis. Comparison between the treatment groups may be made to, in part, support Elidah's selection of a preferred configuration for eventual product commercialization. However, this case series study is not designed to allow rigorous statistical analysis between the groups.

Electrical stimulation is known to have a positive effect on both UUI, and some women have difficulty distinguishing between UUI and SUI episodes. Accordingly, in an effort accurately capture the totality any therapeutic improvement, the study's **primary outcome measure** of efficacy is a change in total urinary incontinence (UI) leaks, both SUI and UUI. Each adherent subject's Daily Log will be used to determine the average number of urinary incontinence episodes per day for the baseline and 6th week (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 6th week assessments refer to the first and last 5 entries in the Daily Log. The percent reduction in UI episodes is then calculated for each patient by subtracting the final week average from the baseline average, dividing the difference by the baseline average, and multiplying by 100. The percent reductions for each patient are then used to define an average (and standard deviation) reduction for each treatment group.

UI episodes per day data may additionally be reported as a responder rate. FDA guidance suggests that subjects with a percent reduction of ≥50% be considered responders. Accordingly, the responder rate for each treatment group will be calculated by dividing the number of subjects with a reduction of ≥50% by the total number of subjects.

Secondary outcome measures will similarly use descriptive statistics (e.g. mean, standard deviation) to characterize changes from baseline. Additionally, where applicable, FDA suggested response rate thresholds will be referenced. Notes on specific secondary outcome measures include:

- **Change in urgency episodes with a leak** – UUI leak data will be analyzed in the same manner as the primary outcome measure data.
- **Change in urgency episodes without a leak** – Differences in mobility, activity, etc. may impact whether a subject can get to a toilet before an urgency leak occurs. Analysis of episodes without leaks will occur in the same manner as the "with leak" data.
- **Change in pad use** - Reduction in pad usage will be assessed as a percent change relative to the baseline, and as a response rate, wherein a 50% reduction is considered clinically significant. Subjects who do not use a pad during the baseline week will be excluded from the analysis.
- **Change in daily bathroom visits / Change in nighttime bathroom visits** – Descriptive statistics as defined above.
- **I-QoL** – Incontinence 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.

Usability surveys will solicit subject feedback pertaining to their experience with the product. Appropriate statistical methods will be used in reporting these subjective measures.

In addition to characterizing outcome measures as a change in value/score (i.e. percent reduction) or a clinically meaningful response (e.g. ≥50% change), 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-UUI device. Elidah may pool data from both treatment groups if there is demonstrated homogeneity between the subject groups and the outcome measures.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Subjects will provide data using the following forms:

- Pre-Study Questionnaire (TR-1155-FORM-1)
- I-QoL Questionnaire (TR-1155-FORM-2)
- Daily Log (TR-1155-FORM-3)
- Post-Study Questionnaire (TR-1155-FORM-4)

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-UUI controller and ELITONE accessories (see 6.4)
- ELITONE electrodes (see 6.3)
- User Manual (TR-1155-FORM-12)
- Pre-paid postage and packaging

Upon completion of the study, subjects are required to return the controller so that study staff can download saved treatment data. Elidah will reconcile components on the Case Report Form (TR-1155-FORM-10). After the controller is inspected it will be returned to the subject.

10.3 Specimen Management

No biological specimens are collected as part of this study

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.

EMS and TENS devices (including the ELITONE device) are sold over the counter and used in an at-home environment. Given the high degree of similarity between those devices and the ELITONE-UUI 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-1155-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-1155-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-1155-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-1155-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-1155-FORM-1 – Pre-Study Questionnaire
- TR-1155-FORM-2 – I-QoL Questionnaire
- TR-1155-FORM-3 – Daily Log
- TR-1155-FORM-4 – Post-Study Questionnaire
- TR-1155-FORM-5 – Informed Consent Form
- TR-1155-FORM-6 – Enrollment Log
- TR-1155-FORM-7 – Subject Code Log
- TR-1155-FORM-8 – Protocol Deviation Log
- TR-1155-FORM-9 – Adverse Event Log
- TR-1155-FORM-10 – Case Report File
- TR-1155-FORM-11 – Screening Log
- TR-1155-FORM-12 – User Manual
- TR-1155-FORM-13 – Screening Questions
- TR-1155-FORM-14 – Candidate Recruitment Language
- TR-1155-FORM-15 – Subject Instructions

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