Clinical Evaluation of Perineal Electrical Stimulation for Urinary Incontinence in Men

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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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Summary of Most Recent Revision:

2.2 Primary Endpoint: pre-treatment measurement now defined during the week before use of treatment device.

4.1 Inclusion Criteria: Arm A: Scheduled for robotic assisted laparoscopic prostatectomy, Arm B: has had prostatectomy, at screening, not post-op screening

4.2 Exclusion Criteria: Arm A: Has had prior prostate radiation

4.5 Retention Strategies: Subjects wll be compensated with $100 (up to $250 for Arm A)

5.1 Study Type: Case series with two treatment groups

5.2 Number of Subjects: 20 subjects for Arm B

5.3 Evaluations: Follow-up will be optional in Arm B

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1. Executive Summary

1.1 Objectives

The primary objective is to demonstrate the safety and efficacy of the Elidah device for male urinary incontinence.

1.2 Design and Outcomes

This is a case series. Pre- and post-study outcome measures evaluate the change in incontinence episodes as measured primarily by pad weight, and secondarily by pad usage, urgency, nocturia episodes, and quality of life. An additional secondary outcome is change in sexual health.

1.3 Interventions and Duration

Participants will self-administer electrical stimulation using the Elidah device, 20 minutes per session, 5x per week for 6 weeks. The study device is identical to Elidah's Elitone device, however the transcutaneous electrode is configured for male anatomy.

1.4 Sample Size and Population

The population includes men ages 21-80 soon after radical robotic-assisted laparoscopic prostatectomy. The goal is to have 30 men complete the study.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

The primary objective of this study is to demonstrate the safety and efficacy of the Elidah device as a conservative treatment for post-prostatectomy male incontinence.

2.2 Primary Endpoint

Treatment efficacy is assessed by comparing the average 24-hr pad weight at the end of treatment to the corresponding pre-treatment weight, whereas the pre-treatment is measured the week before use of treatment device.

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

2.3 Hypothesis

This case series is not a hypothesis driven study. The expectation is that the Elitone device, FDA cleared to treat stress incontinence in women, will similarly treat stress incontinence in males and realize a clinically meaningful reduction (≥50%) in urinary incontinence relative to a pre-treatment baseline. Secondary measures may also show clinically meaningful changes.

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 (OTC) 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
- Sexual health (SHIM)
- Usability Data (e.g. Ease of Use, Satisfaction, Preferred Intensity Settings)
- Treatment Compliance
- Nocturia
- Stress Incontinence Leaking episodes
- Urgency episodes
- Comfort

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 5 men over age 60. Although most of incontinence in men is due to overactive bladder, a significant portion of stress urinary incontinence is related to radical prostatectomy(SUI). Up to 60% of men experience persistent urinary incontinence after prostatectomy (depending on definition). It has a significant impact on quality of life, impact on return to work and activities and time to continence is one of the most frequently asked post-op questions.[1]

With an estimated 233,000 new cases per year, prostate cancer stands out as the predominant cancer diagnosed in men across the United States.[2,3] The diagnosis of prostate cancer often occurs at localized stages, ensuring a positive long-term prognosis for most patients. The combination of prostatectomy (surgical removal of the prostate) and/or radiation therapy commonly leads to a lasting cure in the majority of cases with localized prostate cancer. However, that also leads to a very large cohort of men experiencing long-term complications, which could have an impact on their overall quality of life. (QoL)[4]. Thus, effective control of side effects is vital for defining the success of treatment and bolstering the well-being of prostate cancer survivors.

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[1] Mariotti G, Sciarra A, Gentilucci A, Salciccia S, Alfarone A, Di Pierro G, Gentile V. Early recovery of urinary continence after radical prostatectomy using early pelvic floor electrical stimulation and biofeedback associated treatment. J Urol. 2009 Apr;181(4):1788-93. doi: 10.1016/j.juro.2008.11.104. Epub 2009 Feb 23. PMID: 19233390.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018, 68(6):394-424.

[3] Siegel RL, Miller KD, Fuchs HE, Jemal A: Cancer statistics, 2022. CA Cancer J Clin 2022, 72(1):7-33.

[4] Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, Blazeby JM, Peters TJ, Holding P, Bonnington S et al: Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med 2016, 375(15):1425-1437.

Although spontaneous recovery of incontinence often occurs, and there is sufficient evidence to suggest that pelvic floor muscle exercises can help treat incontinence in men as well as women,[5] 44.5% still experience symptoms one year after surgery, and it can take one to two years to fully regain control.[6] Any improvement in speed of recovery could have a significant impact in the lives of these men.

Electrical muscle stimulation (EMS) essentially assists in performing pelvic floor muscle exercises in a stronger fashion. EMS elicits repeated contractions to regain strength of the pelvic floor muscles needed for continence. In a RCT, the use of electrical stimulation therapy (perineal or anal) proved to be significantly superior to the sole physiotherapeutic continence training alone.[7] For men, EMS has been offered as an anal probe (Incontrol Medical's InToneMV, Skylark Device & Systems Co.'s Skylark Uro Probe, Innovamed-USA's Detrusan 500, and many more). However, none are currently available, likely due to the lack of acceptance. Perineal EMS showed significantly higher acceptance and a lower rate of side effects and was superior in quantifiable incontinence parameters when compared to intra-anal application. This was attributed to better user compliance.[7]

Urinary continence in men is directly related to the internal (smooth muscle) and external (striated) sphincter muscles. The prostate also contributes to increased outlet resistance, especially as men age and the prostate enlarges. After radical prostatectomy, the internal sphincter at the bladder neck is removed and the patient's continence becomes dependent on the external urinary sphincter. Due to the fact that the external sphincter is a striated muscle it can fatigue, especially after the insult of prostatectomy. Fortunately, the striated muscle can be rehabilitated and strengthened and continence can be improved.

3.2 Study Rationale

Transcutaneous 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).*[8]

There is a long history of use of intravaginal EMS for treatment of SUI in women, and it is predicated on the assumption that proximity of the electrodes to the pelvic floor and bladder is of primary importance. 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

[5] Aydın Sayılan A, Özbaş A. The Effect of Pelvic Floor Muscle Training On Incontinence Problems After Radical Prostatectomy. Am J Mens Health. 2018 Jul;12(4):1007-1015. doi: 10.1177/1557988318757242. Epub 2018 Mar 14. PMID: 29540090; PMCID: PMC6131443.

[6] Van Kampen M, De Weerdt W, Van Poppel H, De Ridder D, Feys H, Baert L. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. Lancet. 2000 Jan 8;355(9198):98-102. doi: 10.1016/S0140-6736(99)03473-X. PMID: 10675166.

[7] Hoffmann, W., Liedke, S., Dombo, O. et al. Die Elektrostimulation in der Therapie der postoperativen Harninkontinenz. Urologe [A] 44, 33–40 (2005).

[8] 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

treating SUI and UUI.[9,10,11,12] Building on these findings, Elidah developed a wearable, use-at-home SUI-specific EMS device called Elitone for women. 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 for women in 2019.

Elidah now seeks to evaluate the device in men with urinary incontinence. Although the device is not only for men post-prostatectomy, this patient population presents a large cohort of men with a common etiology for their urinary incontinence who would benefit from quicker return of urinary continence.

The Elitone® device (Elidah, Monroe, Connecticut) delivers electrical muscle stimulation (EMS) through the perineal region to stimulate the pelvic floor muscles and surrounding structures. Electrical stimulation is generated by a wearable, battery-powered control unit connected to the electrode via a short cable. The control unit provides an interface that allows the patient to initiate treatment and set the stimulation intensity at a desirable level. The device delivers a defined treatment regimen comprising 4 seconds of stimulation at 50 Hz, 2 seconds of stimulation at 10 Hz, and 6 seconds of relaxation (i.e., no output), after which the cycle is repeated for a total of 20 minutes. Throughout treatment, the user has the ability to increment or decrement the stimulation intensity, and after 20 minutes the device turns off automatically.

Elitone is FDA-cleared for the treatment of female stress UI, based on a clinical trial (NCT04752709), demonstrating significant improvement in incontinence symptoms across multiple outcome measures. Of the trial participants, 95% of patients treated with the device achieved a reduction in the number of leaks per day, with an average reduction of 71% after 6 weeks of use. Pad usage and QoL measures improved significantly for 85% and 67% of treated patients, respectively.

Recently, the device was developed for use in men. The Elidah device utilizes the same components as the Elitone® device with an electrode component (GelPad) that has been adapted for use in men. In the current study, we will describe the efficacy of the Elidah treatment on male urinary incontinence.

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

[9] Oh-oka H, "Efficacy of interferential low frequency therapy for elderly wet overactive bladder patients", Indian Journal of Urology, 2008;24(2):178-181..

[10] Dougall DS, "The effects of interferential therapy on incontinence and frequency of micturition", Physiotherapy, 1985;71(3):135-136.

[11] Switzer, D; Hendriks, O, "Interferential therapy for the treatment of stress and urge incontinence", Irish Medical Journal, 1988;8(1):30-31.

[12] Ferreira APS, Pegorare ABGsS, Salgado PR, Casafus FS, Christofoletti G, "Impact of a pelvic floor training program among women with multiple sclerosis: A controlled clinical trial", Am J Phys Med Rehabil., 2016;95(1):1-8

on a case-by-case basis prior to enrolling the subject, and documented in the subject's Case Report Form (TR-1168-FORM-10).

- Age: 18-80y
- Gender: Male
- Scheduled for or within 4 weeks (Arm A) or has had (Arm B) robotic assisted laparoscopic prostatectomy
- Read and speak English
- (screening) Predominant stress urinary incontinence as determined by responses to a series of three standard questions defined as:
    - An affirmative response to "Do you lose urine with physical activities such as coughing, sneezing, lifting something heavy?",
    - 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, an affirmative response to "Are more of your incontinence episodes due to physical activities rather than a strong urge to urinate?"
- (screening) Use of 1 or more pads/day average (also checked during baseline)

4.2 Exclusion Criteria.

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

- History or symptoms of urinary incontinence, urinary retention, extra-urethral incontinence, overflow incontinence
- Complete denervation of the pelvic floor
- Severe Obesity as defined by BMI >= 40
- Has undergone pre-op pelvic floor exercise strengthening
- Pelvic pain/painful bladder syndrome
- Implanted cardiac device, untreated cardiac arrhythmia or suffer from other heart problems.
- History of epilepsy
- Underlying neurologic/neuromuscular disorder
- Metal implants in the abdomen or pelvic area
- Chronic coughing
- Impaired decision making, suicidal thoughts, or drug/alcohol dependence
- Uncontrolled intercurrent illness that would limit compliance with study requirements
- Lacks capacity to adhere with study requirements
- Lacks capacity to consent for themselves.
- Has had prior prostate radiation (Arm A)

4.3 Study Enrollment Procedures

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

Recruitment

- Healthcare providers who are 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.
- Ads placed in social media and other forums to attract candidates to a website that describes the study. These ads will be placed in the US without regional geographic targeting and use key words including “incontinence” and “bladder leaks” and “prostate cancer surgery” or “prostatectomy.”

Screening

- Interested candidates complete an online survey comprising Screening Questions (TR-1168-FORM-1)
- Responses are maintained electronically 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.
- Note: Two screening questions regarding leakage are asked or confirmed post-operative.

Consent

- Candidates that meet the enrollment criteria based on responses to the screening survey will be directed to an informational session regarding study requirements (online, video, or direct contact)
- Study personnel can 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-1168-FORM-10) if enrolled, or in the screening log if not enrolled.
- Consent documentation (TR-1168-FORM-7) is sent to the candidate either electronically or as a hardcopy.
- The candidate returns the signed consent form, or via an online option.
- The consent will be countersigned, once the final pre-op screening questions are confirmed.
- The candidate is now considered a “subject”, and a sequential Subject Number is assigned, and Case Report file started.
- A copy of the signed consent document is maintained in the subject’s Case Report File.

Treatment Initiation

- Study materials and training videos are sent to the subject (see 10.1 and 10.2)

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 men from across the US, which additionally encourages participation from a diverse pool of candidates.
- Subjects will have access to the Elidah device which retails for $399.

4.5 Retention Strategies

- Subjects will be compensated with $100 (up to $250 for Arm A) and the study device returned (if elected). 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

30 subjects in Arm A, 20 subjects in Arm B. Appreciating that some subjects who are initially enrolled will fail to complete treatment and return the study materials, it is likely that 60-70 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.[13] 24-hour pad weight 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.

- **Pre-Study Incontinence History and Usability Questionnaire** (Baseline) – 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-1168-FORM-2). 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) and again on the 12th week. Among other items, they log their treatment completion (Y/N), treatment intensity (0-35), and number of pads used (TR-1168-FORM-5). 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 6th week.
- **24-Hour Pad Weight Test** (Baseline and Post-study, Follow-Up (Arm A, optional Arm B))

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

– 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.[14] Subjects may wear whichever pads they prefer, but need to weigh and record a single dry one. 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 weigh the bag. 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, subjects will be required to take 3 measurements during the pre- and post-study periods.

- **I-QoL Questionnaire** (Baseline and Post-study) – the Incontinence Quality of Life (I-QoL) questionnaire is a validated tool for assessing changes in the degree to which urinary incontinence affects quality of life (TR-1168-FORM-3). 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 completed electronically (see 10.4).
- **Sexual Health Inventory for Men (SHIM)** (Baseline and Post-study) – SHIM is a validated tool for the screening and diagnosis of erectile dysfunction in clinical practice and research. The tool is commonly used to monitor improvement in erectile function with intervention. The questionnaire is composed of 5 questions, to which the participant provides information relating to erections and sexual intercourse. Each selection has a corresponding score and the scores, and the total scores are summed. The sum results in a score that describes the severity of erectile dysfunction.
- **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-1168-FORM-6).
- **Follow-up Questionnaire/Log (@12 weeks) – T**he follow-up questionnaire will ask about pad usage, leaking, quality of life, and any continued device usage (TR-1168-FORM-13).

5.4 Adverse Events (Throughout Study)

The study comprises five stages: Pre-study, Baseline, Treatment, Post-Study, and Follow-Up– See 7.3.Protocol Schedule

- **Pre-Study** – The subjects are screened to qualify. Their history is taken, study is explained, and consent is obtained. Training videos may be watched during this time.
- **Baseline** – Concurrently, the subjects maintain the Daily Log for 7 days to establish a baseline of pad weights and pads/day measures. The pre-study, I-Qol and SHIM questionnaires are taken during this week, and 3 measurements of 24-hr pad weights are taken. No treatment is administered during this period. Subjects are instructed that they should not perform baseline activity if they are ill. All data will be on electronic platforms.
- **Treatment** – Subjects will self-administer treatment with the Elidah 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 during the 6th study week they are instructed to extend treatment for at least

[14] 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.

5 days after they are in good health. During the treatment weeks subjects are required to maintain their Daily Log.

- **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.
    - The device may be returned to the subject at his request.
- **Follow-up** – At 12 weeks (Arm A, optional Arm B), follow-up questionnaire will be sent to the subject including questions regarding pad usage, leakage, quality of life, and any continued device usage. A daily log and 3x measurement of 24-hr pad weight will be taken.

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

● - Data used in primary and secondary endpoint analysis ▯ - Used to establish compliance.	Pre-Study Questionnaire	I-QoL Questionnaire	SHIM Questionnaire	3x Pad Weight measurements	Number of Self-administered Treatment	Daily Log	Post-Study Usability Questionnaire	Follow-up questionnaire + 3x Pad Weight Measurement	Adverse Events
Pre-Study (Screening /History /Consent/ Training)									
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	●			●
Post-Study Data		●	●	●			●		●
Follow-up Data (Week 12)				●		●		●	

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-1168-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-1168-FORM-10), including the name of the medication, dosage, route of administration, date, and indication for use.

5.7 Blinding

There is no blinding in this study.

6. Elidah DEVICE

6.1 Device History

The Elidah device has been evaluated clinically in prior IRB approved studies (WIRB-20162650, WIRB 20180640). 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 Elidah.

6.2 Description of Treatment Regimen

The Elidah 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 6weeks. 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.

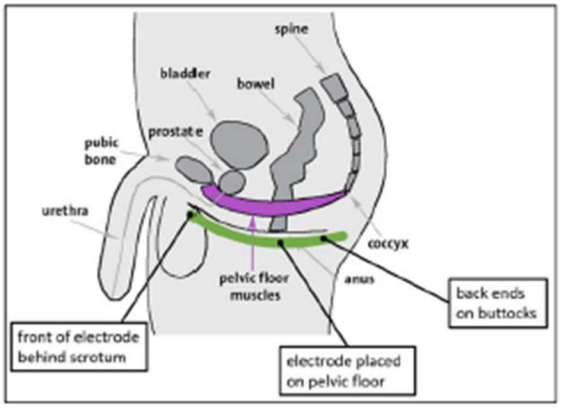


Figure 6-1: Rendering of Elidah device worn on the male anatomy, under clothing.

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: Patient contacting side of electrode component, including conductive regions (blue)

The electrodes are packaged in quantities of five in a resealable pouch. They are identified as part number EE-1012, 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(TR-1168-FORM-11), belt clip and product packaging.

6.5 Other Study Materials

Electronic Scale – As a part of the study materials, an electronic scale with instructions will be delivered to the study subject.

Pads – Choice and type of pad will be supplied by the subject. We will ask that they weigh one dry pad of the same type.

Hair Trimmer – A groin hair trimmer may optionally be offered and requested as needed.



Figure 6-3: Elidah Controller and all accessories, including the User Manual (not shown), GelPad Cable, Charging Cable, Belt-Clip (attached to Controller) and device packaging.

6.6 Stimulation Waveform

The Elidah 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.

6.7 Control/Sham Device

There is no control/sham group in this study

6.8 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 Elidah device for men.

6.9 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 Elidah product is identical to the commercially available Elidah 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 Elidah device and the proposed protocol present low risk to the subjects. This assessment is supported by the following information:

- **Equivalence to the Elidah Device** – There is no difference between the Elidah device controller (software) and the FDA cleared, commercially available Elitone device controller.
- **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 Elidah 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 Elidah 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-1168-FORM-11)

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 Elidah due to the anatomic-specific nature of the Elidah 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-1168-FORM-11) identifies applicable warnings 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 subjects 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 Elidah 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 Elidah 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 Elidah 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 to achieve a measurable result.

- From Sand *et al*[15] 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.
- From Richardson *et al*[16], 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.

[15] 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.

[16] 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.

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, Elidah will aim to enroll 30 subjects. See 9.4 regarding interim analysis and stopping rules.

9.2 Randomization

Subjects are not randomized.

9.3 Blinding

Subjects and staff members interacting with those subjects are not blinded.

9.4 Interim Analyses and Stopping Rules

Due to the short duration of the study (6 weeks) and likely rapid enrollment (1-2 months), 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.

9.5 Data Analyses

This is not a hypothesis driven study. Descriptive statistics will be the primary means of data analysis.

Electrical stimulation is known to have a positive effect on incontinence. Accordingly, in an effort to accurately capture the totality of any therapeutic improvement, the study's **primary outcome measure** of efficacy is an average of 3 measurements taken over the week, each measuring the weight of pads over 24 hours. Each adherent subject's Daily Log will be used to determine the average number of urinary incontinence episodes, separating urgency 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 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 metric.

Improvement 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 metric 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 stress incontinence episodes**– As possible, this data will be used in relation to urgency data.
- **Change in urgency episodes**– Differences in mobility, activity, etc. may impact whether a subject can get to a toilet before an urgency leak occurs.
- **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 or average less than 1 pad/day during the baseline week will be excluded from the analysis.
- **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.
- **SHIM** – Improvement in SHIM scores.

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.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Subjects will provide data using the following forms:

- Pre-Study Questionnaire (TR-1168-FORM-2)
- I-QoL Questionnaire (TR-1168-FORM-3)
- SHIM Questionnaire (TR-1168-FORM-4)
- Daily Log (TR-1168-FORM-5)
- Post-Study Questionnaire (TR-1168-FORM-6)

The forms are sent to the subjects in hardcopy and the 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:

- Elidah controller and Elidah accessories (see 6.4)
- Elidah electrodes (see 6.3)
- User Manual (TR-1168-FORM-11)
- Pre-paid postage and packaging
- Scale and bags

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-1168-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 use of the device.

EMS and TENS devices (including the Elidah device) are sold over the counter and used in an at-home environment. Given the high degree of similarity between those devices and the Elidah 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 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-1168-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-1168-FORM-7 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, which is maintained within the study binders (see 10.4).

Once the subject is enrolled, her name is entered into the Enrollment Log. 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.

12. APPENDICES

(As separate documents)

- TR-1168-FORM-1 – Screening Questions
- TR-1168-FORM-2 – Pre-Study Questionnaire
- TR-1168-FORM-3 – I-QoL Questionnaire
- TR-1168-FORM-4 – SHIM Questionnaire
- TR-1168-FORM-5 – Daily Log
- TR-1168-FORM-6 – Post-Study Questionnaire
- TR-1168-FORM-7 – Informed Consent Form
- TR-1168-FORM-8 – Protocol Deviation Log
- TR-1168-FORM-9 – Adverse Event Log
- TR-1168-FORM-10 – Case Report File
- TR-1168-FORM-11 – User Manual
- TR-1168-FORM-12 – Subject Instructions
- TR-1168-FORM-13 – Follow-up Questionnaire/Log