Original Application for an Investigational Device Exemption

19 July 2017

Subcutaneous Tibial Nerve Stimulation for Urgency Urinary Incontinence

Device Name: eCoin (Electroceutical Coin)

Protocol Number: 111-3186
IDE Number: G170028
NCT03029624

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CONFIDENTIAL
Document Number 111-3186 Rev. 1.6

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1 Introduction

1-1 *Name, Address, and Signature of Sponsor*

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1-2 *Overview*

Overactive bladder (OAB) is a clinical diagnosis characterized by the presence of bothersome urinary symptoms including urgency, frequency, nocturia, and urgency incontinence. Urinary incontinence is a prevalent condition that markedly impacts quality of life affecting both men and women (1). In population based studies, the prevalence of OAB ranges from 7% to 27% in men, and 9% to 43% in women (2-9). However, urgency urinary incontinence, characterized by involuntary leakage of urine that is associated with a sudden compelling desire to void, is more common in women. Because urgency urinary incontinence can be difficult to distinguish from stress urinary incontinence, total incontinence episodes are often measured in the clinical trial setting. Suffering from unpredictable loss of urine and associated odor or related symptoms, the burden on quality of life is well documented.

While physical therapy and surgery are relatively effective treatments for stress urinary incontinence, disorders of the detrusor muscle and/or neural regulation of the lower urinary tract system remain quite challenging to treat well. There are a number of treatments including first line behavioral therapies and second line medications (anti-muscarinics or oral β_3-adrenoceptor agonists), but many patients remain in poor control. For those not well treated by behavioral therapy or medications, or intolerant of medications, percutaneous tibial nerve stimulation (PTNS) as well as sacral nerve stimulation (SNS) are approved for marketing by the National Institutute for Health and Clinical Excellence (NICE) in the United Kingdom and by the Food and Drug Administration in the United States. In the US, PTNS is cleared for treatment of overactive bladder and the associated symptoms of urinary frequency, urinary urgency and urinary urge incontinence. Furthermore, a category I CPT code was approved by

the Centers for Medicare and Medicaid Services (effective Jan. 1, 2011). Percutaneous tibial nerve stimulation, described by Stoller in the late 1990s, has been documented in a large number of medium sized clinical studies for the treatment of overactive bladder. For PTNS, given the need for maintenance therapy over the long-term (10), the expense of such maintenance visits, and waning efficacy of the therapy when conducted in the home (11), the use of a tiny fully-implantable device is likely to have advantages in implementation. Such advantages may include automated compliance, lower cost over device life compared with long term visit costs, and improved efficacy through accurate device placement by visualization of tibial nerve compared with percutaneous administration at home.

1. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. Jama 1998;280:1995-2000.
2. Choo MS, Ku JH, Lee JB et al: Cross-cultural differences for adapting overactive bladder symptoms: results of an epidemiologic survey in Korea. World J Uro 2007; **25**: 505.
3. Corcos J and Schick E: Prevalence of overactive bladder and incontinence in Canada. Can J Urol 2004; **11**: 2278.
4. Coyne KS, Sexton CC, Vats V et al: National community prevalence of overactive bladder in the United States stratified by sex and age. Urology 2011; **77**: 1081.
5. Tikkinen, KA, Auvinen A, Tiitinen A. et al: Reproductive factors associated with nocturia and urinary urgency inin women: A population-based study in Finland. Am J Obstet Gynecol 2008: **199**: 153 e1.
6. Irwin DE, Milsom I, Hunskaar S et al: Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: Results of the EPIC study. Eur Urol 2006; **50**: 1306.
7. Stewart WF, Van Rooyen JB, Cundiff GW et al: Prevalence and burden of overactive bladder in the United States. World J Uro 2003; **20**: 327.
8. Herschorn S, Gajewski J, Schulz J, et al: A population-based study of urinary symptoms and incontinence: The Canadian Urinary Bladder Survery. BJU Int 2008; **101**; 52.
9. Milsom I, Abrams P, Cardozo L et al: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Intl 2001; **87**: 760.
10. Yoong, Wai, et al. "Neuromodulative treatment with percutaneous tibial nerve stimulation for intractable detrusor instability: outcomes following a shortened 6-week protocol." *BJU international* 106.11 (2010): 1673-1676.
11. van der Pal F, van Balken MR, Heesakkers JP, et al: Percutaneous tibial nerve stimulation in the treatment of refractory overactive bladder syndrome: is maintenance treatment necessary? BJU Int 2006, 97(3):547–550.

2 Report of Prior Investigations

2-1 *Prior Publications of Animal Studies*

The underlying science in support of tibial nerve stimulation for treatment of overactive bladder has been well described in published scientific literature. For example, in 1966, McPherson first demonstrated in a cat model that stimulation of the cut ends of dorsal spinal roots or various peripheral nerves including the posterior tibial nerve can effectively inhibit bladder contractions (12). The hypothesis for this effect was an action of neural circuitry in the forebrain, as intercollicular decerebration or thoracic spinal cord transection abolished the effect (13). Later, in 1980, Sato et al. verified that electrical stimulation of afferent nerves to hind limb muscles, but not cutaneous afferents, inhibited reflex bladder activity in the anesthetized cat (14). Three years later, McGuire and Morrissey used electrical stimulation of the hindquarter nerves to treat detrusor instability in spinal injured nonhuman primates before moving onto demonstrate such effect in the clinical setting in 16 patients (15). Next, case studies were conducted and then a number of randomized, controlled trials.

The tibial nerve is a mixed nerve comprised of sensory and motor nerve fibers. It is by action of central afferent fibers that neuromodulation of the tibial nerve works to restore normal control of an imbalanced voiding reflex. It is the large diameter somatic afferent fibers of the tibial nerve that cause inhibition of bladder activity by way of central inhibition of the micturition reflex pathway in the spinal cord or the brain. Such is confirmed by studies in anaesthetized female cats (14). Neuromodulation of the tibial nerve is presumed to improve or restore normal control of an imbalanced voiding reflex by action of the central afferents (12, 17). Thus, the therapy aims to cause detrusor inhibition by acute electrical stimulation of afferent tibial nerve fibers. Interestingly, it appears that the same spinal roots (L4-S3) are targeted by both sacral nerve stimulation and tibial nerve stimulation. It appears that stimulation of the sacral roots, sacral nerve, pudendal nerve and tibial nerve all affect central components of the neural circuits controlling the bladder, yet we can deduce some distinctions in the action. That is, a study by Tai and colleagues shows that short duration stimulation of the tibial nerve causes a persistent post-stimulation inhibition and increase of bladder capacity (18) that is replicated by many tibial nerve clinical studies, yet the effects of sacral nerve stimulation are shown to go away once stimulation is stopped (19).

As the bladder is controlled by sympathetic, parasympathetic, and somatic nervous systems that are regulated by the pontine micturition center (PMC), it is likely that tibial nerve stimulation acts on the PMC, either via the pelvic nerve or pudendal nerve or both. Bladder contraction (micturition) is controlled via the pelvic nerve (S2-S4) and continence is controlled via the hypogastric nerve (T10-L2) and the pudendal nerve (L4-S3); it is thereby deduced that stimulation of the large somatic afferent fibers of the tibial nerve, with spinal roots from L4-S3, finds its effect on the bladder via either the pelvic or the pudendal nerve.

12. McPherson A. The effects of somatic stimuli on the bladder in the cat. J Physiol. 1966;185(1):185–96.
13. McPherson A. Vesico-somatic reflexes in the chronic spinal cat. J Physiol. 1966;185(1):197–204.PubMed

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16. van der Pal, F., M. van Balken, and J. Heesakkers. "Maintenance percutaneous tibial nerve stimulation (PTNS) treatment in successfully treated patients with refractory overactive bladder syndrome: a necessity."*Eur Urol* 47.Suppl 4 (2005): 144.
17. Vandoninck, Vera, et al. "Posterior tibial nerve stimulation in the treatment of urge incontinence." *Neurourology and urodynamics* 22.1 (2003): 17-23.
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19. Herbison GP, Arnold EP. Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. Cochrane Database Syst Rev. 2009; Suppl 2:CD004202. doi:10.1002/14651858.CD004202.pub2
20. Oerlemans, Dennis JAJ, and Philip EV Van Kerrebroeck. "Sacral nerve stimulation for neuromodulation of the lower urinary tract." *Continence*. Springer London, 2009. 217-226.

2-2 *Human Studies*

2-2-1 Prior Publications of Tibial Nerve Stimulation for Overactive Bladder

Inhibition of detrusor activity by peripheral neuromodulation of the posterior tibial nerve was first described by McGuire et al. (21) and more recent authors such as Govier et al. (22), van Balken et al. (23) and Vandoninck et al. (24) have confirmed a 60–80% positive response rate after 12 weekly treatments with percutaneous tibial nerve stimulation. According to a meta-analysis by Gaziev et al. (25), level 1 evidence is available and supportive of the safety and efficacy of tibial nerve stimulation for overactive bladder. Data available on the safety of percutaneous tibial nerve stimulation shows no major concerns for safety. For example, in the 24 month follow up study to the SUmiT trial, the authors find there were no reported treatment related adverse events in the 50 subjects through 24 months (26). Four subjects reported five adverse events with unknown causes (UTI, pulling feeling on feet, bladder pressure, pinched nerve and slow stream).

21. McGuire, E. J., et al. "Treatment of motor and sensory detrusor instability by electrical stimulation." *The Journal of urology* 129.1 (1983): 78-79.
22. Govier, Fred E., et al. "Percutaneous afferent neuromodulation for the refractory overactive bladder: results of a multicenter study." *The Journal of urology* 165.4 (2001): 1193-1198.
23. van Balken, Michael R., et al. "Posterior tibial nerve stimulation as neuromodulative treatment of lower urinary tract dysfunction." *The Journal of urology* 166.3 (2001): 914-918.
24. Vandoninck, Vera, et al. "Posterior tibial nerve stimulation in the treatment of urge incontinence." *Neurourology and urodynamics* 22.1 (2003): 17-23.
25. Gaziev, Gabriele, et al. "Percutaneous tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review." *BMC urology* 13.1 (2013): 1.

26. Peters, Kenneth M., et al. "Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial." *The Journal of urology* 183.4 (2010): 1438-1443.
27. Finazzi-Agrò, Enrico, et al. "Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: a randomized, double-blind, placebo controlled trial." *The Journal of urology*184.5 (2010): 2001-2006.
28. Amarenco, G., et al. "Urodynamic effect of acute transcutaneous posterior tibial nerve stimulation in overactive bladder." *The Journal of urology* 169.6 (2003): 2210-2215.
29. Peters, Kenneth M., et al. "Sustained therapeutic effects of percutaneous tibial nerve stimulation: 24-month results of the STEP study." *Neurourology and urodynamics* 32.1 (2013): 24-29.

2-2-2 Prior Studies of the Valencia Technologies eCoin System

The Valencia Technologies eCoin system is currently in the final months of follow-up in a prospective, multicenter study to confirm the effectiveness and safety of median nerve stimulation using bilateral eCoin devices in resistant or drug intolerant hypertensive human subjects. The proposed study for this investigational device exemption addresses a different underlying condition from that previously tested with eCoin. Rather, urinary urge incontinence treated with tibial nerve stimulation by eCoin is proposed. Thus, only safety data from previous nerve stimulation studies of the eCoin system is presented herein.

2-2-2-1 Safety

Among the 48 subjects with 96 implanted eCoin devices, there have been no device or therapy related Serious Adverse Events.

Nine subjects have experienced inflammation tenderness or redness at the incision site or hand. Four subjects have been treated for an infection at the implant site. One of these infections occurred after six months post implant and led to the explant of the device. Three out of the four infections were from one clinical center which was subsequently shut down at the recommendation of the DSMB. One additional explant of a device occurred at this same center due to an unconfirmed infection. All remaining Adverse Events were thought to be unrelated to the device or therapy.

The case report forms for the four reported infections are in Attachment 4-12. In addition, a fifth case report form is included for what the DSMB regarded as an infection leading to explant that was not appropriately handled by the center in Ottawa, Canada (Site 12).

The five subject adverse events with infection or explant can be summarized as follows: 12-005 reported moderate bilateral device infection resolved with antibiotics; 04-008 reported severe left arm infection treated initially with antibiotics, but ultimately resulting in explantation of device from the left arm; 14-006 self-reported mild small infection for a few days that resolved on its own; 12-007 reported mild right forearm infection that resolved with antibiotics; and 12-004 reported middle finger cellulitis initially treated with antibiotics, but ultimately resulting in explantation of device from the right arm. The corresponding adverse event logs, organized according to patient number, are enclosed.

The DSMB investigation into the higher than average infection at Site 12 found that the Site was not timely in its filing of adverse event reports; and pointed out that the AE on 12-004 stated that the patient's swollen middle finger was observed on the very day of implantation. After discussions with site 12 the DSMB was unconvinced that Site 12 had put in place an effective plan for confronting its high infection rate. The DSMB recommended suspension of implantation at Site 12 (see attached letter from DSMB – Attachment 4-13). After discussions with the Principal Investigator at Site 12, the Company decided to suspend indefinitely any further implantations at Site 12.

2-2-2-2 Conclusions

Adverse events related to the eCoin therapy are primarily associated with inflammation or infection at the implant site. There have been no device related serious adverse events.

2-3 *Executive Summary of Non-Clinical Studies*

Preclinical testing of the eCoin subcutaneous neuromodulation system has been performed to assure conformance to the design specifications.

The eCoin subcutaneous neuromodulation system was developed under an ISO 14971:2012 compliant risk management process to identify potential harms and to eliminate risk or reduce risks to an acceptable level.

2-3-1 Bench Testing - eCoin Device

The eCoin device is designed to be compliant with all applicable clauses of ISO 14708-1:2014 Implants for surgery – Active implantable medical devices – Part 1: General requirements for safety, marking and for information to be provided by the manufacturer and ISO 14708-3:2008 Active implantable medical devices -- Part 3: Implantable neurostimulators.

2-3-1-1 Stimulus Output (207-1093 2.2.1-2.2.5, 2.3.1; 207-1082 2.1-2.5, 2.8)

The stimulation output pulse amplitude, current regulation (at loads of 300, 600, 1000, 1500, and 2500 Ohms), pulse width and pulse rate of the eCoin device were verified at room temperature, 20 °C, and 45 °C and over battery voltages of 2.7 V, 3 V and 3.2 V.

Folder: “VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports”

File: “004_207-1093 SNS Design Verification Test Report.” Refer to Sections 2.2.1-2.2.5 and 2.3.1.

File: “003_207-1082 SNS PCBA Verification Test Report.” Refer to Sections 2.1-2.5 and 2.8.

2-3-1-2 Internal Moisture (207-1093 2.3.2, 2.3.3)

Residual gas analysis was performed to verify the internal moisture of the hermetically sealed eCoin device is no more than 1.5%. This test was repeated on eCoin devices after 24 hour water immersion at 80 °C water and a pressure of 2 atm.

Folder: “VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports”

File: “004_207-1093 SNS Design Verification Test Report.” Refer to Sections 2.3.2 and 2.3.3.

2-3-1-3 Temperature Exposure (207-1093 2.3.4, 202-1254)

The eCoin device in a sterile pack passed final functional test after one hour of temperature exposure at -10 °C and 55 °C per ISO 14708-3 clause 26.2. In addition as part of the packaging validation, eCoin devices passed functional test after exposure to climatic conditioning per ASTM D4332-13.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.4.

Folder: "VOL_020_IDE Attachment 4-18 Sterile Packaging Validation Report"

File: "001_4.18 202-1254 SNS Device Packaging Validation Report"

2-3-1-4 Pressure Exposure (207-1093 2.3.5)

The eCoin device passed final functional test after one hour of pressure exposure at 70 kPa and 150 kPa per ISO 14708-1:2014 clause 25.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.5.

2-3-1-5 Random Vibration (207-1093 2.3.7)

The eCoin device passed final functional test after random vibration at 5 Hz to 500 Hz for 30 minutes in each of three mutually perpendicular axes per ISO 14708-1:2014 clause 23.2.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to section 2.3.7.

2-3-1-6 Mechanical Shock (207-1093 2.3.8)

The eCoin device passed final functional test after mechanical shock per ISO 14708-1:2014 clause 23.7 (1 ms duration 500 g half-sine).

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.8.

2-3-1-7 Mechanical Squeeze Test (207-1093 2.3.9)

The eCoin device passed final functional test following a ten minute exposure to a force of 45 N applied to the top center of the device over an area of 0.5 cm squared.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.9.

2-3-1-8 Battery UL Testing (EA1821)

The eCoin device battery passed testing per UL 1642 5th edition including short circuit (room temperature and 55 °C), abnormal charging, crush, impact, shock, vibration, heating, temperature cycling, low pressure and projectile.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "013_EA1821_RPT_Valencia CR1612_UL1642."

2-3-1-9 Battery External Short Test (207-1093 2.3.12)

The eCoin device battery under an external short circuit fault condition was verified to generate less than a 2 °C temperature rise at the device surface when implanted subcutaneously (ISO 14708-3:2008 clause 17.1).

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File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.12.

2-3-1-10 Electrocautery Immunity Test (207-1093 2.3.13)

The eCoin device passed final functional test following a 10 second exposure to a conducted 500 kHz since wave delivering 10 V peak to peak between the anode and cathode approximating the signal from monopolar electrocautery applied no closer than 25 cm from the eCoin device.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.13.

2-3-1-11 Corrosion Test (207-1093 2.4.1)

No corrosion of the eCoin case, feed through anode or cathode in phosphate buffered physiological saline at 37 °C was observed after continuous stimulation at maximum amplitude until battery depletion.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.4.1.

2-3-1-12 Battery Service Life and Elective Replacement (207-1082 2.6, 2.7; 201-1016, 201-1111)

The eCoin battery discharge current and accelerated battery discharge capacity at 37 °C were used to verify a 2 year service life at nominal amplitude after a 12 month shelf life and a 1 year elective replacement at the maximum amplitude after a 12 month shelf life.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File 1: "003_207-1082 SNS PCBA Verification Test Report." Refer to Sections 2.6 and 2.7.

File 2: "022_ER 201-1016 Rev 1 - CR1612 Battery"

File 3: "023_ER 201-1111 Rev 1 – CR1612 Battery Discharge Capacity RIR 419-356"

2-3-1-13 Accelerated Life Test (207-1082 2.9)

The eCoin electronics assembly (PCBA) passed final functional test following a highly accelerated life test (HALT) at 125 °C for 1000 hours while under power with a supply voltage of 3.2 volts.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "003_207-1082 SNS PCBA Verification Test Report." Refer to Section 2.9.

2-3-1-14 Temperature Cycling Test (207-1082 2.10)

The eCoin electronics assembly (PCBA) passed final functional test following temperature cycling test per MIL-STD-883H Method 1010, Condition B (10 cycles, -55 +0/-10 degrees Centigrade to 125 +15/-0 degrees Centigrade, 10 minute dwell time minimum).

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "003_207-1082 SNS PCBA Verification Test Report." Refer to Section 2.10.

2-3-1-15 Laser Seam Weld Validation (202-1436)

The eCoin device laser seam weld process was validated (IQ, OQ, PQ) to demonstrate that it produces a reliable hermetic seam weld. Acceptance criteria included visual inspection, fine leak, gross leak and cross section for weld penetration.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "001_202-1436 PVR SNS Device Seam Weld Top Cover and Feed thru Case."

2-3-2 Bench Testing External Controller

The External Controller is designed to be compliant with all applicable clauses of AAMI / ANSI ES60601-1:2005/(R) 2012 and A1:2012, c1:2009/(R) 2012 and a2:2010/(r) 2012 (consolidated text) Medical Electrical Equipment – Part 1: General requirements for basic safety and essential performance, IEC 60601-1-2:2014 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic disturbances - Requirements and tests.

2-3-2-1 External Controller Output (207-1541 4.2.1- 4.2.8)

The External Controller was verified to meet all output command and command data transmission and timing requirements.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.2.1 – 4.2.8.

2-3-2-2 External Controller Battery Discharge and Charge Time (207-1541 4.2.9, 4.2.10)

The External Controller was verified to provide at least 7 days of standby operation and 15 minutes of transmit operation on a single battery charge. The External Controller charging with fully discharged battery was verified to complete within 6 hours.

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File: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.2.9 and 4.2.10.

2-3-2-3 External Controller Battery Safety Testing (RSZBHST 160325326, VTC-002A (IEC 60950-1 4.3.8), 207-1541 4.2.11 – 4.2.13, 4.2.15)

The External Controller rechargeable Li-polymer battery has undergone safety testing and passed per IEC62133:2012. In addition, the battery protection circuitry for over-charging, over-discharge, and over-heating were verified to operate as specified. Battery short-circuit protection was verified to operate as specified and also passed testing per IEC 60950-1 4.3.8.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File 1: "014_005_RSZBHST 160325326."

File 2: "021_External Controller Safety Testing VTC_002A IEC 60601-1 3rd ed Ec01 Remote."

File 3: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.2.11 – 4.2.13 and 4.2.15.

2-3-2-4 External Controller Over-heat Shutdown (207-1541 4.3.2, 4.3.3)

The External Controller has been verified to shut-down transmission if the temperature of the device exceeds 48 °C.

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File: "005_207-1541 SNS External Controller Verification Test Report." Refer to Sections 4.3.2 and 4.3.3.

2-3-2-5 External Controller IEC 60601-1 (VTC-002A)

The External Controller has passed applicable clauses of IEC 60601-1: 2005 + CORR. 1 (2006) + CORR. 2 (2007) + AM1 (2012) or IEC 60601-1: 2012. This includes clauses 5.7 Humidity, 8.7 Leakage Current, 8.8.3 Dielectric Strength, 8.8.4.1 Enclosure Ball Pressure Test, 11.1.1 Excessive Temperatures, 11.6.1 Cleaning, Sterilization Disinfection and 15.3 Mechanical Strength (Push, Drop and Mould Stress Relief).

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "021_External Controller Safety Testing VTC_002A IEC 60601-1 3rd ed Ec01 Remote"

File Attachments: "017_External Controller Safety Testing VTC-002A Attachment A Photographs;" "018_External Controller Safety Testing VTC-002A Attachment B Schematics;" "019_External Controller Safety Testing VTC-002A Attachment C Calibration;" and "020_External Controller Safety Testing VTC-002A Attachment D Specifications."

2-3-3 MR Compatibility

The eCoin Subcutaneous Neuromodulation System has not been evaluated for safety and compatibility in the MRI environment and is considered MRI unsafe. Patients with the eCoin implant should not undergo Magnetic Resonance Imaging (MRI).

2-3-4 Electrical Safety and Electromagnetic Compatibility

2-3-4-1 Electromagnetic Non-Ionizing Radiation Immunity (SD72116479-0516, 207-1093 2.3.6)

The eCoin device passed final functional test after and remained immune during exposure to electromagnetic non-Ionizing radiation per ISO 14708-3 Clause 27.

Folder: "VOL_018_IDE 4-16 Design Verification and Validation Reports"

File 1: "016_SD72116479-0516-0516 CISPR 11 Class B ESD and ISO14708-3 Test Report." Refer to Section 4.

File 2: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.6.

2-3-4-2 Current Leakage (207-1093 2.3.10)

The direct current leakage between the anode and cathode of the eCoin was verified to be less than less than 0.75 microamperes / square millimeter of electrode surface per ISO 14708-3 clause 16.2. Notes: For a direct current leakage less than 1 microampere, the 4.0 ±0.2mm diameter cathode current density is less than 0.08 microamperes per mm-squared. The cathode is worst case since it has a smaller surface area than the anode.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.10.

2-3-4-3 Insulation Leakage (207-1093 2.3.11)

After preconditioning by total immersion into 9 g/l saline at 37 °C for at least 10 days, the eCoin insulation at maximum stimulation amplitude was verified to be greater than 3.3 kOhm based on no more than a 10% reduction in amplitude when the load is reduced from 600 Ohms to 300 Ohms (measured greater than 30 kOhm).

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "004_207-1093 SNS Design Verification Test Report." Refer to Section 2.3.11.

2-3-4-4 Electrostatic Discharge (SD72116479-0516)

The eCoin device passed final functional test and demonstrated safe operation after exposure to electrostatic discharge per IEC 61000-4-2 up to ± 8 kV direct contact and up to ± 15 kV air discharge.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "016_SD72116479-0516 CISPR 11 Class B ESD and ISO14708-3 Test Report." Refer to Section 3.1.

2-3-5 Electrical Safety and EMC External Controller

2-3-5-1 Electromagnetic Emissions and Non-Ionizing Radiation Immunity (SD72110544-1015)

The External Controller has undergone testing and passed EMC emissions and immunity per IEC 60601-1-2:2014. This includes radiated and conducted emissions per CISPR 11 Class B, harmonic current emissions per EN61000-3-2 Class A and voltage fluctuations and flicker per EN 61000-3-3. Immunity testing includes electrostatic discharge per IEC 61000-4-2, amplitude modulated RF EM fields per IEC 61000-4-3, proximity RF fields from wireless communication equipment per IEC 61000-4-3, electrical fast transients per IEC 61000-4-4, surge per IEC 61000-4-5, RF common mode per IEC 61000-4-6, power magnetic field of 30 A/m at 50Hz and 60 Hz per IEC 61000-4-8 and voltage dip and interruptions per IEC 61000-4-11.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "015_SD72110544-1015 External Controller EMC Test Report." Refer to Section 3.

2-3-6 Software eCoin Device (209-1035, 209-1061, 303-1122)

The level of safety concern for the eCoin device firmware is Moderate since a failure or latent design flaw could directly result in a minor injury to the patient by leading to uncomfortable levels of stimulation and/or the need for premature device explant.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File 1: "006_209-1035 SNS Firmware Verification Test Report"

File 2: "007_209-1061 Firmware Unit Test Report" (plus 008_209-1061 Appendix A & 009_209-1061 Appendix B)

File 3: "024_209-3264 Rev 1 - SNS Firmware Verification Test Report OAB"

Folder: "VOL_028_IDE Attachment 4-26 303-1122 Software Design Specification SNS"

File: "001_4.26 303-1122 Software Design Specification SNS."

2-3-7 Software External Controller (207-1541, 303-1122)

The level of safety concern for the External Controller firmware is Minor since its function is limited such that a failure or design flaw is unlikely to cause any injury to the patient or operator. Verification and validation testing has been completed with all software design requirements met.

Folder: "VOL_018 IDE Attachment 4-16 Design Verification and Validation Reports"

File: "005_207-1541 SNS External Controller Verification Test Report."

Folder: "VOL_028_IDE Attachment 4-26 303-1122 Software Design Specification SNS"

File: "001_4.26 303-1122 Software Design Specification SNS."

2-3-8 Biocompatibility

2-3-8-1 Cytotoxicity ISO 10993-5 (PBL 14E0355G-M01G)

Based on the qualitative evaluation of cells exposed to eCoin test article extract, the eCoin test article was not considered to have a cytotoxic effect (no reactivity).

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports"

File: "001_Cytotoxicity Pacific BioLabs Study No. 14E0355G-M01G."

2-3-8-2 Sensitization ISO 10993-10 (PBL 14H0049G-X01G)

Under the conditions of the study, the eCoin test article did not elicit sensitization reactions.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports"

File: "002_Report Sensitization Pacific BioLabs Study No 14H0049G-X01G."

2-3-8-3 Irritation ISO 10993-10 (PBL 14H0048G-X01G)

Based on erythema and edema scores, no irritation was noted with the eCoin test article when compared to control. Under the conditions of the study, the eCoin test article met the requirements for the Intracutaneous (Intradermal) Reactivity Test.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports"

File: "003_Irritation Pacific BioLabs Study No 14H0048G-X01G."

2-3-8-4 Acute Systemic Toxicity ISO 10993-11 (PBL 14H0051G-X01G)

None of the animals treated with eCoin test article extract exhibited a greater biological activity when compared to those treated with the control. Under the conditions of the study, the eCoin test article met the requirements of ISO 10993-11.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports"

File: "004_Acute Systemic Toxicity Pacific BioLabs Study No 14H0051G-X01G."

2-3-8-5 Sub-Chronic Systemic Toxicity 90 Day ISO 10993-6 (PBL 16C0069G-X01G)

The results suggest that the device, when implanted subcutaneously was well-tolerated in male and female Sprague Dawley rats over a period of 94 days. There was no evidence of test article effect on body weights and body weight changes. Changes in several hematology and clinical chemistry parameters that reached statistical significance were not considered test article related because they appeared to be sporadic and values were within the normal range typical for this animal species. There were no statistically significant differences in coagulation factors.
There were no microscopic observations in the systemic tissues or organs of male and female rats that were considered to be related to the subcutaneous implantation of the test article. There were two notable lesions that were identified macroscopically in two female rats from the test group; a lump present near the implant site (Animal #13) and right eye opacity (Animal # 12). The lesion near the implant site observed in one female animal was identified as M-adenocarcinoma of mammary gland and was considered incidental. The ocular changes observed in Animal #12 were considered to be of a traumatic etiology. The local, subcutaneous tissue response to both the control article and test article was comparable for male and female rats as characterized primarily by fibrosis, neovascularization, and cellular infiltrates.

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports"

File: "005_Sub-chronic Toxicity Pacific BioLabs Study No. 16C0069G-X01G."

2-3-8-6 Genotoxicity ISO 10993-3 (PBL 14E0349G-X01G, 16E0213G-X01G)

Based on the criteria and conditions the Bacterial Mutagenicity Test (Ames Assay) used, the eCoin test article was considered non-mutagenic. In a ISO 10993-3:2014 compliant mouse lymphoma assay, the mutant frequencies and cloning efficiencies of preparations treated with the eCoin test article were within limits defined for a negative response. Accordingly, the eCoin is considered to be non-mutagenic and non-clastogenic in the mouse lymphoma assay test system.

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports"

File 1: "006_Genotoxicity AMES PBL No 14E0349G-X01G."

File 2: "007_Genotoxicity Mouse Lymphoma 16E0213G-X01G."

2-3-8-7 Implantation 90 Day ISO 10993-6 (PBL 14E0356G-X01G)

Under the conditions of the study, the eCoin test article was considered a non-irritant to the tissue as compared to the negative control article.

Folder: "VOL_029 IDE Attachment 4-27 Biocompatibility Reports"

File: "008_Implantation Pacific BioLabs Study No. 14E0356G-X01G."

2-3-8-8 Pyrogen - Material Mediated ISO 10993-11 (PBL 16C0182G-X01G)

The test was performed according to ISO 10993-11 and USP <151> guidelines. All animals appeared healthy during the test and none of the tested rabbits exhibited individual increase in temperature greater or equal to 0.5°C when compared to the control temperature. Based on criteria for this test, the test article meets USP <151> requirements for the absence of pyrogens

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports"

File: "009_Material-Mediated Pyrogenicity 16C0182G-X01G."

2-3-8-9 Ethylene Oxide Sterilization Residuals ISO 10993-7 (Nelson 749416)

The ethylene oxide residual for the eCoin device was less than 0.012 mg (1.2 micrograms per centimeter squared of device surface area). The ethylene chlorohydrin residual for the eCoin device was less than 0.038 mg (3.8 micrograms per centimeter squared of device surface area). Both of these are within the ISO 10993-7 limit for permanent implants and the tolerable contact limit.

Folder: "VOL_029_IDE Attachment 4-27 Biocompatibility Reports"

File: "010_EO Residuals 749416 8XL."

2-3-9 Particulate (Nelson Lab Number 884283-01)

The eCoin device particulate counts meet requirements per ISO 14708-1:2014 clause 14.2.

Folder: "VOL_018_IDE Attachment 4-16 Design Verification and Validation Reports"

File: "010_884283-S01 Particulate Test."

2-3-10 Sterility (2002-1206)

The eCoin device ethylene oxide sterilization process was validated per ISO 11135 using half cycle batch release approach using the over kill method (ISO 11135-1:2007(E) Annex B).

Folder: "VOL_019_IDE Attachment 4-17 Ethylene Oxide Sterilization Validation Reports"

File: "001_Ethylene Oxide Sterilization Validation Reports"

2-3-11 Packaging (202-1254; Westpak 225-15-0053A)

Validation of the eCoin device packaging demonstrated that the integrity of the final package is maintained under the severities of distribution, storage and handling. After 3x (worst case) sterilization, baseline samples were tested for seal strength per ASTM F88M:2009 and seal integrity per ASTM F1886-09. Remaining samples underwent climatic conditioning followed by shipping and handling testing per ASTM D4169-14. Zero-aged samples were then tested for seal strength per ASTM F88M:2009 and seal integrity per ASTM F1886-09. Remaining samples underwent accelerated and real time shelf-life aging (see 2-3-12).

Folder: "VOL_020_IDE Attachment 4-18 Sterile Packaging Validation Report"

File 1: "001_202-1254 SNS Device Packaging Validation Report."

File 2: "003_Appendix B Test Lab Report No 225-15-0053A"

2-3-12 Shelf Life (202-1254; Westpak 225-15-0053B, 225-15-0053C)

Accelerated and real time aging of the eCoin device and its packaging demonstrated that the integrity of the final package and device functionality is maintained over the 1 year device shelf-life. Accelerated aging equivalent to a 13 month shelf life was completed per ASTM F1980-07. Real-time aging for 13 months was completed at ambient conditions (approximately 25 °C and 50% relative humidity). After aging, packaging samples were then tested for seal strength per ASTM F88M:2009 and seal integrity per ASTM F1886-09 and the eCoin device underwent final functional testing.

Folder: "VOL_020_IDE Attachment 4-18 Sterile Packaging Validation Report"

File 1: "001_202-1254 SNS Device Packaging Validation Report"

File 2: "004_Appendix C Test Lab Report No 225-15-0053B."

File 3: "005_Appendix C Test Lab Report No 225-15-0053C 13 Month Real Time Aging of the SNS."

3 Investigational Plan

3-1 *Purpose*

The investigation is a feasibility study of the safety and efficacy of the Valencia Technologies eCoin system in the treatment of urgency urinary incontinence in patients with refractory overactive bladder. The study will be completed in 16 months.

The primary aims are to evaluate the change in urgency incontinence episodes in patients after 3 months of tibial nerve stimulation therapy with eCoin and the safety of eCoin during the same period.

3-2 *Summary*

This trial is a single arm, prospective study of the safety and effectiveness of eCoin tibial nerve stimulation in subjects with refractory overactive bladder as defined by the American Urological Association (30). The eCoin neuromodulation device will be implanted subcutaneously in the right or left leg of patients with urgency urinary incontinence. After a 4 week implant healing period, subjects will have their devices activated (turned ON). After 3 months of device therapy (occurring 4 months post-implant), the primary endpoint will be assessed. It is anticipated that subjects will reach the full therapeutic effect at approximately 3 months of therapy. Subjects will be followed for an additional 9 months to assess the safety of maintenance stimulation therapy with fewer sessions occurring during this time interval.

30. American Urological Association, OVERACTIVE BLADDER DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER IN ADULTS AUASUFU Guideline (2012); Amended (2014).

3-3 *Protocol*

3-3-1 Study Design

The study is a single arm, prospective study of the safety and effectiveness of the Valencia Technologies eCoin System to stimulate the tibial nerve for the treatment of patients with refractory urgency urinary incontinence.

3-3-2 Subject Selection

3-3-2-1 Patient Population

The primary sample size target is 50 subjects with refractory urgency urinary incontinence. For enrollment, eligible subjects will be consented and entered into a baseline evaluation period to confirm study eligibility with a baseline assessment including complete medical history, physical examination, and completion of a 3-day voiding diary to quantify voiding behavior, symptoms, and incontinence. Subjects with presence of clinically significant bladder outlet obstruction, positive urine cytology, positive urine culture, and documented neurogenic bladder dysfunction will be excluded. Only subjects who meet all the inclusion and exclusion criteria, and have provided informed consent, will be enrolled. It is estimated that approximately 100 subjects will be enrolled into baseline evaluation in order to yield 50 implanted subjects (where up to 35 subjects in the United States will be implanted).

All eligible enrolled subjects are implanted with the eCoin system after baseline assessment. The implantation side will be left to the discretion of the investigator. Approximately 4 weeks post implantation, subjects will return for implant activation at which time the device will be activated and therapy will begin. A programming technician will implement the activation procedure, setting amplitude of stimulation according to the upper level of a subject's comfort.

3-3-2-2 Selection Criteria

Participants shall be screened in accordance with the following inclusion and exclusion criteria.

3-3-2-2-1 *Inclusion Criteria*

1. Women and men 18 years and older.
2. Diagnosis of overactive bladder with urgency urinary incontinence or mixed urge and stress incontinence with a predominant urgency component, for at least 6 months (self-reported).
3. Individual has at least one urgency incontinence episode, on average over a one-day period, as determined over a 3-day period.
4. Individual is unresponsive to, inadequately responsive to, or intolerant of behavioral, rehabilitation, and pharmacologic therapy.
5. Individual is able to give his or her written, informed consent.
6. Individual is mentally competent and able to understand all study requirements.
7. Individual is willing and able to complete a 3-day voiding diary and quality of life questionnaire.
8. Individual is without pharmacological treatment of overactive bladder (antimuscarinics and beta-3 agonists) for 2 weeks prior to baseline.

3-3-2-2-2 *Exclusion Criteria*

1. Individual has predominantly stress urinary incontinence.
2. Individual has clinically significant bladder outlet obstruction.
3. Individual has clinically significant pelvic organ prolapse.
4. Individual has abnormal post void residual (i.e., greater than 150 cc).
5. Individual has clinically significant urethral stricture disease or bladder neck contracture.
6. Individual has an active urinary tract infection at time of enrollment.
7. Individual has recurrent urinary tract infections defined as 4 or more UTI's per year.
8. Individual has peripheral arterial disease.
9. Individual has chronic venous insufficiency with a history of skin change (hyperpigmentation, lipodermatosclerosis, ulceration) in the ankle region.
10. Individual has morbid obesity.
11. Individual has had positive urine cytology or diagnosis of bladder or prostate cancer.
12. Individual has neurogenic bladder dysfunction.
13. Individual is taking an alpha-blocker for benign prostatic hyperplasia.
14. Individual is pregnant or intends to become pregnant during the study.
15. Patient is breast feeding or is less than 9-month post-partum.
16. Individual has the presence of urinary fistula, bladder stone, or interstitial cystitis.
17. Individual has uncontrolled diabetes mellitus.
18. Individual has an implanted device.
19. Individual has been previously treated with sacral nerve stimulation.
20. Individual has been treated with onabotulinumtoxinA in the previous 9 months prior to enrollment.
21. Individual has been treated with percutaneous tibial nerve stimulation within the previous 12 weeks prior to enrollment.
22. Individual is aware that he or she will need an MRI scan during the study period.
23. Individual has a clotting or bleeding disorder; antiplatelet and anticoagulant therapy may be continued or held at the discretion of the investigator.
24. Individual has a clinically significant peripheral neuropathy.
25. Individual is neutropenic or immunocompromised.
26. Individual has had previous surgery and/or significant scarring at the implant location.
27. Individual has ongoing dermatologic condition at the implant site, including but not limited to dermatitis and autoimmune disorders.

3-3-3 Ethical Considerations

No critical ethical issues have been identified. Subjects who are refractory to available drug therapy have the potential to gain a new treatment modality through participation in the study and to assess the impact of this treatment modality on their incontinence with minimal risk. However, the following are considerations:

- Some subjects may not receive clinical benefit from eCoin therapy, but are to continue with follow-ups until study completion. Note that in some cases, benefit may be identified over time based on late response and cumulative effects of treatment.
- Subjects are intended to be without pharmacological medications for overactive bladder. If the addition of medications is medically necessary as described herein, such changes may affect a subject's continued participation in the study.

3-4 *Study Procedures*

All subjects will be followed for 6 months post-activation: collecting a 3-day voiding diary reporting the number of incontinence episodes, number of micturitions, voided volumes, and quality of life scores at 1, 2, 3, 4 and 6 months post-activation.

All subjects are expected to remain free of pharmacological medications for overactive bladder, unless medically necessary, until the primary endpoint measured at 3 months post-activation. Subjects who are taking pharmacologic medication should be washed off OAB medications for a period of 2 weeks prior to baseline.

After the 3 month post-activation study endpoint has been reached, all subjects will be monitored at 12 months post-activation.

At 12 months, the study is concluded.

3-4-1 Subject Recruitment Plans

Investigators will identify patients currently under their direct care, and contact patients that appear to qualify from medical records. Investigators will also seek referrals from other urology, urogynecology, and gynecology practices. A member of the site's clinical research team shall assess whether the individual seems suitable for the study. The patient should have a medical history of overactive bladder with urgency incontinence. Patients with urgency incontinence who appear to meet the inclusion/exclusion criteria from medical records will be contacted by the Investigator or designated study staff and presented with the opportunity to participate in the study, including:

- reason for being identified (refractory urgency urinary incontinence)
- therapy description
- potential benefits
- risks
- compensation (see 3-12-5)

If the patient is interested thereafter, they will be brought into the research clinic for further screening and informed consent.

3-4-2 Visit Overview

The ordered enrollment process consists of screening including obtaining written consent, completing the baseline evaluation, implantation of eCoin system, and establishing the stimulation paradigm for the patient. A flowchart depicting the process is provided in Figure 1. The timing of visits 1 through 4 is described in relationship to the immediately previous visit, while the timing of visits 6 through 10 is described in relationship to visit 5 (the activation).

For visits involving a 3-day diary, the diary should be completed over 3 consecutive days during the 7 days prior to each indicated visit. The site should give patients a call to remind them of the diary requirement at least 3 days prior to each follow up visit.

- Visit 1: Screening Procedures (informed consent, urinalysis, PVR, history and physical examination, subjects begin 2 week wash-off of OAB medications if applicable, concomitant medication therapy review, eligibility determination)
- Visit 2: Baseline Assessments (3-day voiding diary, I-QoL, subject sent home with 7-day TENS trial instructions) (Time: Between 0 and 28 days from Visit 1)
- Visit 3: Implant Procedure (Time: Between 0 and 14 days from Visit 2)
- Visit 4: Incision Healing Check (week 2) (Time: Between 9 and 19 days from Visit 3)
- Visit 5: Activation (week 4) (Time: Between 23 and 33 days from Visit 3)
- Visit 6 (1 month post-activation): Follow up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including I-QoL, patient satisfaction, and patient global assessment of improvement) (Time: Between 23 and 33 days from Visit 5)
- Visit 7 (2 months post-activation): Follow up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including I-QoL, patient satisfaction, and patient global assessment of improvement) (Time: Between 51 and 61 days from Visit 5)
- Visit 8 (3 months post-activation): Follow up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including I-QoL, patient satisfaction, and patient global assessment of improvement) (Time: Between 79 and 89 days from Visit 5)
- Visit 9 (4 months post-activation): Follow up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including I-QoL, patient satisfaction, and patient global assessment of improvement) (Time: Between 107 and 117 days from Visit 5)
- Visit 10 (6 months post-activation): Follow up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including I-QoL, patient satisfaction, and patient global assessment of improvement) (Time: Between 163 and 173 days from Visit 5)
- Visit 11 (12 months post-activation): Follow up Assessments (3-day voiding diary, adverse event assessment, concomitant medication therapy review, patient surveys including I-QoL, patient satisfaction, and patient global assessment of improvement) (Time: Between 331 and 341 days from Visit 5)
- Visit 12 (12 months post-activation): Explantation to follow Visit 11 (Time: On or within 30 days of Visit 11)
- Visit 13 Incision Healing check (2 weeks post-explantation): visit to assess wound healing. (Time: Between 9 and 19 days post-explantation).

	Screening	Baseline	Implantation	Incision Healing Check	Activation (Follow up Clock Starts)	1 Month Follow-up	2 Month Follow-Up	3 Month Follow-Up: Primary Endpoint	4 Month Follow-Up	6 Month Follow-up	12 Month Monitoring	Incision Healing Check
Demographics, screening exam, physical exam, & medical history	X											
Eligibility Determination	X	X										
Informed Consent	X											
3-day Voiding Diary Reminder Call	X	X	X				X	X	X	X	X	
3-day Voiding Diary	X	X	X				X	X	X	X	X	
Post Void Residual (PVR)	X											
Urinalysis		X										
I-QoL Assessment		X					X	X	X	X	X	
7-day TENS Trial Data Collection			X									
Patient Reported Satisfaction Assessment							X	X	X	X	X	
Patient Global Impression of Improvement							X	X	X	X	X	
Implant or Explant Procedure			X								X	
Incision Assessment				X								X
Activation					X							
Completion of Primary Endpoints								X				
Completion of Study												X
Subject Assessment for AEs			X	X	X	X	X	X	X	X	X	X

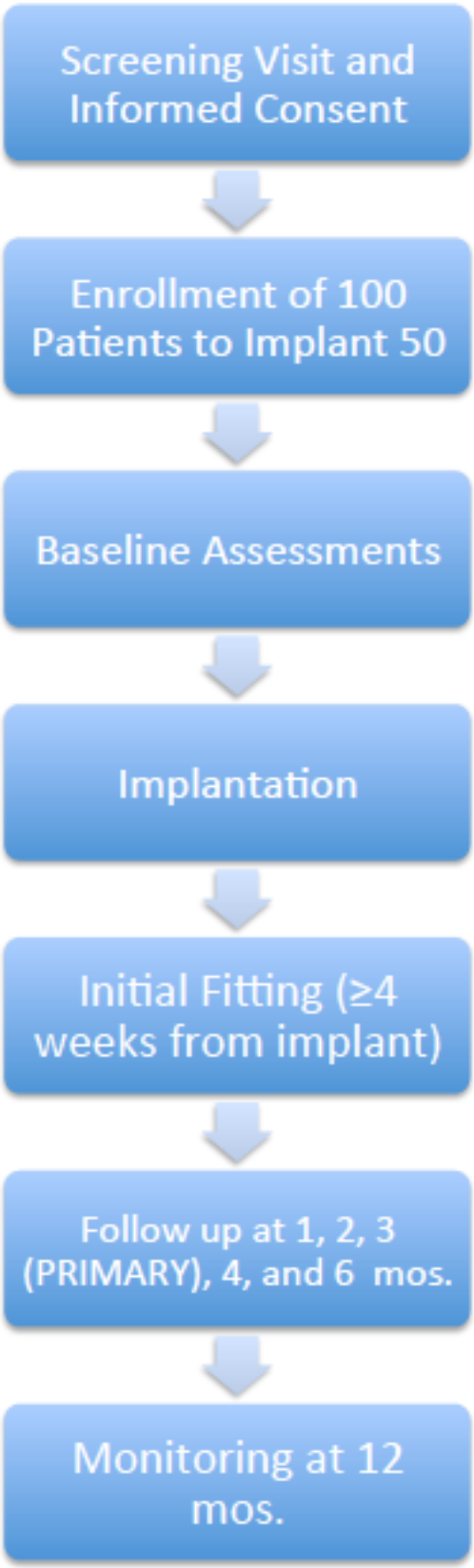

Screening Visit and Informed Consent
Enrollment of 100 Patients to Implant 50
Baseline Assessments
Implantation
Initial Fitting (≥4 weeks from implant)
Follow up at 1, 2, 3 (PRIMARY), 4, and 6 mos.
Monitoring at 12 mos.

Figure 3-1: Summary of Study Process

3-4-3 Screening for Eligibility Procedures

Interested adults who are known or present at the research site with refractory urgency urinary incontinence may be initially screened for inclusion in the study. Patients' medical records will be reviewed for inclusion/exclusion criteria.

Patients who initially qualify will be scheduled for a screening visit to assess general health and overactive bladder condition. Urinalysis will be utilized after providing their informed consent. Patients will also be questioned for inclusion/exclusion criteria in addition to medical record review. A history will be taken, physical exam will be performed, and general health to participate in the study will be further evaluated by the Investigator at the screening visit.

3-4-4 Prior and Concomitant Therapy

The intent of the study is to enroll subjects who are refractory to other modes of therapy, including behavioral therapy, pelvic floor exercises, and pharmacologic therapy. Subjects who are taking pharmacologic agents for overactive bladder or other agents that may influence urination at enrollment will be expected to discontinue those medications at least 2 weeks prior to baseline. Subjects who are not taking such agents will be expected to remain agent-free until the primary endpoint, A complete list of prescription drugs, over-the-counter drugs, or dietary supplements should be taken at screening to ensure stability of medications that can affect urination.

3-4-5 Informed Consent Procedures

The study as contained in the Informed Consent (see Attachment 4-5) will be presented to the individual for consideration at the screening visit. The individual will be given adequate time to have all questions answered and to carefully consider participation. If, after understanding the purpose, potential risks, potential benefits, and requirements of the study, as well as his or her rights as a research participant, the individual agrees to participate as evidenced by providing written informed consent, the subject will be enrolled to enter the baseline period. The subject should be allowed to take informed consent documents home for further consideration, if needed, and scheduled with an additional visit to complete the screening visit. Informed Consent shall be included in the patient's medical record file and noted in the screening CRF.

3-4-6 Baseline Visit Assessments

At the conclusion of the Screening Visit, eligible subjects who have provided informed consent will be asked to come back for baseline assessments.

Baseline assessments will include:

1) 3-day voiding diary;
2) I-QoL assessment;
3) TENS trial instructions;

Study staff will schedule subject's implantation procedure to follow baseline assessments.

3-4-7 TENS Trial

At baseline, subjects will be sent home with a TENS (transcutaneous electrical nerve stimulation) unit and instructions to perform TENS of the tibial nerve twice daily for seven days. The electrical paradigm will be preset to match the electrical paradigm of eCoin (pulse width of 0.2 ms and frequency of 20 Hz), but the subject will set the amplitude of stimulation to the upper level of comfort. Subjects should perform one thirty minute session in the morning and one in the evening for 7 days (total of 14 sessions). Subjects will also be asked to complete a voiding diary in the last three days of the TENS trial. This TENS trial will occur after the baseline visit but before the implantation visit. The purpose of this trial is to ascertain whether there is a relationship between responders to TENS and responders to eCoin therapy. Patients will not be excluded from participation in this study based on response to TENS. This procedure is optional in New Zealand.

3-4-8 Implantation of Subcutaneous Neuromodulation System

An implant procedure is to be completed following, but no later than 30 days from, the baseline visit. The eCoin system will be implanted in accordance with the procedures outlined in the Surgical Implant Manual set forth in Attachment 0. The implant procedure is conducted as an outpatient procedure under local anesthesia for subcutaneous placement. An incision site healing check will be performed 2 weeks post implant. Subjects will be provided a minimum of 4 weeks for healing prior to activation of the system.

Prior to discharge from the procedure, the research staff shall review study requirements with the subject to help ensure compliance with the follow-up schedule. All patients will be required to return to clinic for an incision assessment visit, one activation visit, one safety assessment visit, three follow up visits, followed by one long-term maintenance visit as outlined in the protocol. Telephone numbers will be obtained from the participant at the time of informed consent to ensure the clinic has the ability to contact the subject and primary physician as needed. Patients will be instructed on post-procedural care and activities, and antibiotics and pain medication will be prescribed at the discretion of the investigator.

3-4-9 eCoin Activation

Four weeks after implantation, subjects will return for device activation. All subjects will have their device activated.

The subject will be provided with a 3-day voiding diary to complete in the 7 days prior to the next visits (occurring 1, 2, 3, 4, 6, and 12 months post-activation). Subjects will be reminded by phone by a member of the study staff at least 3 days prior to the next visit that they should begin the 3-day diary. Instructions will be given regarding wound care.

3-4-10 Establishment of the Electrical Regimen

The programming technician will follow programming procedures setting the amplitude according to the subject's upper level of comfort. Subjects will be informed that they may periodically feel a tingling or notice a muscle twitch; but if they do, it would be transient and they should not feel anything most of the time, if at all. In particular, subjects may feel a motor response (flexing of the big toe and/or fanning of the other toes) and sensory response (a radiating sensation is felt at the sole of the foot and in the toes).

3-4-11 Post Activation Follow-up Procedure

Subjects will be followed up in visits at 1, 2, 3, 4, and 6 months post activation, with the primary analysis at 3 months.

1) Overactive bladder medications and doses should not be given through the 3 month primary endpoint (unless medication is medically necessary according to the "Escape Treatment" guidelines below).
2) At least 3 days prior to each appointment, the subject will be responsible to complete a 3-day voiding diary to be brought with them to each appointment.
3) Assessments at these follow-up visits are described in the Visit Overview Section 3-4-2.

At the follow-up visit 3 months post-activation, the study endpoint will have been reached. At this time, the addition of medication is allowed if clinically necessary to achieve improved control of overactive bladder symptoms.

3-4-12 Escape Procedure

Overactive bladder medications are not allowed until the study endpoints are reached at 3 months post activation, unless judged medically necessary. Agents added or withdrawn are at the discretion of the Investigator and managing physician(s). Any such adjustments are to be noted on the CRF for the next Follow Up visit.

3-5 *Study Endpoints*

3-5-1 Primary Outcome Measures

3-5-1-1 Primary Effective Outcome Measure

The change in number of incontinence episodes from baseline to three months post-activation.

3-5-1-2 Primary Safety Outcome Measures

Incidence of System and Procedure Related Adverse Events from implantation to one month post-implantation.

Incidence of all Serious Adverse Events from baseline to 3 months post-activation.

3-5-2 Key Secondary Outcome Measure

The percentage of responders in subjects implanted with the device. Responders are defined as subjects with a 50% or greater reduction in urge incontinence episodes from baseline to three months post-activation.

3-5-3 Exploratory Secondary Outcome Measures

The difference in change from baseline in number of incontinence episodes at three and four months post-activation in all responder subjects with data available at three and four month visits.

The change, expressed as a percentage from baseline, in incontinence episodes from baseline to three months post-activation in responder subjects.

The change in number of micturitions from baseline to three months post-activation in responder subjects.

The change in mean voided volume from baseline to three months post-activation in responder subjects.

The change in I-QoL score from baseline to three months post-activation in responder subjects.

The mean change in patient satisfaction score from baseline to 3 months post-activation.

The mean change in patient global impression of improvement score from baseline to 3 months post-activation.

The mean change in quality of life as measured by the IQoL score from baseline to 3 months post-activation.

The proportion of subjects who had a 100% reduction (dryness) in the # of incontinent episodes/24 hours at 3 months post-activation.

3-6 *Rationale for the Selection of Outcome Measures and Study Design*

It is anticipated that eCoin therapy will positively affect a number of symptoms of overactive bladder including number of urge incontinence episodes, voiding volume, frequency, and nocturia. Urinary incontinence is associated with substantial routine care costs and a clinically significant decrement in health-related quality of life that is similar to the impact of other chronic medical conditions like osteoarthritis, chronic obstructive pulmonary disease, and stroke (31). Percutaneous tibial nerve stimulation achieves a 50-70% response rate. Thus, it is anticipated that not all subjects will respond to eCoin therapy, but that a high level of response in responders would translate to a meaningful contribution to overactive bladder care. Thus, the primary outcome focuses on a relatively objective and significant symptom of overactive bladder, the number of incontinence episodes in a 3-day period in responder subjects. Of the secondary outcomes, quality of life is an important measure of the overactive bladder condition because overactive bladder is a symptom-based diagnosis. The degree of bother caused by symptoms directly affects care seeking, treatment intensity, and satisfaction with treatment. However, there has been a historical lack of standardization of such patient reported questionnaires on the quality of life of incontinence patients. Thus, Valencia selected two questionnaires based on evidence that each, the I-QOL and the ICIQ-UI, proved to be valid and reproducible as a self-administered measure for assessing quality of life in patients with urinary incontinence (32, 33).

Given the expected therapeutic equivalence of percutaneous nerve stimulation of the tibial nerve to eCoin stimulation of the tibial nerve, it is not expected that the therapy will cause adverse events. Furthermore, prior experience with eCoin implantation in the forearm for the treatment of hypertension, shows that the primary concern was infection or symptoms of infection, which tend to appear by 30 days post-implantation. Thus, the safety outcomes focus on related events 30 days post-implantation and all serious adverse events through the primary endpoint. In addition, safety will be assessed for an additional 9 months following the primary endpoint assessment.

While an important benefit to the eCoin system is that therapy delivery does not require the patient to operate a percutaneous device and locate the tibial nerve on a regular basis, it is also important to understand how well patients tolerate the device. In order to assess patient acceptance, a patient satisfaction grade will be documented for each subject at 3 months post activation.

31. Schultz SE, Kopec JA. Impact of chronic conditions. Health Rep. 2003;14:41–53.
32. Wagner, T. H., et al. "Quality of life of persons with urinary incontinence: development of a new measure." *Urology* 47.1 (1996): 67-71.
33. Hajebrahimi, Sakineh, et al. "Validity and reliability of the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form and its correlation with urodynamic findings." *Urology journal* 9.4 (2012): 685.

3-7 *Risk Analysis*

3-7-1 Overview

The eCoin system risk assessment (Attachment 4-14) has been completed per FDA-recognized Consensus Standard 5-40: ISO 14971. The risk analysis method identifies each potential hazard which could result in patient harm, with action taken to reduce risk when the risk estimation for any potential hazard exceeds an acceptable level. The risk analysis for the eCoin system and the controller was performed early in the design process and has been updated throughout the process. The identified, anticipated risks were mitigated so that all potential hazards were reduced to an acceptable severity and occurrence.

To verify mitigation of risk, the eCoin system has undergone testing for safety, essential performance, design verification and marking per applicable parts of IEC 60601-1:2005+A1:2012(E) and ISO 14708-1:20000(E) as well as biocompatibility testing to be compliant with all applicable ISO 10993 standards.

The table in attachment 4-15 is a summary of the potential risks to human health and traces them to specific FMEA assignments and risk mitigation measures.

3-7-1-1 Clinical Safety Data as Validation of Risks

The eCoin system has been used in a successful first in human feasibility trial from 2013 through 2016 for the treatment of drug resistant hypertension in adults. The system parameters were 2 pulses per second at a pulse width of 0.5 ms with amplitudes ranging from 0.5 mA to 25 mA. There were no stimulation therapy related adverse events during this study. Section 2-2-2-1 is a summary of the safety results. In this proposed study, the eCoin system parameters will be 20 pulses per second at a pulse width of 0.2 ms with amplitudes ranging from 0.5 mA to 15 mA. The proposed system parameters match that utilized by many percutaneous tibial nerve stimulation studies for which no stimulation related adverse events were reported (3, 13, 17) and the same parameters used by FDA cleared devices (K132561) that also stimulate the tibial nerve for treatment of overactive bladder. According to the American Urological Association's guideline on the diagnosis and treatment of overactive bladder (34), percutaneous tibial nerve stimulation carried minor adverse events in reviewed studies. The most frequently reported events were painful sensation during stimulation that did not interfere with treatment and minor bleeding at the insertion site. In the panel's view, benefits outweigh risks/burdens for the use of percutaneous tibial nerve stimulation in the thoughtfully-selected and counseled patient who is highly motivated to make the office visits required for repeated percutaneous administration of tibial nerve stimulation.

34. Gormley A, Lightner D, Burgio K, Chai T, Clemens JQ, Culkin D, Das A, Foster HE, Scarpero HM, Tessier C, Vasavada SP, Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline. American

Urological Association Education and Research
https://www.auanet.org/education/guidelines/overactive-bladder.cfm

3-7-2 Description of Patient Population

The eCoin system is indicated for the treatment of patients with refractory urgency urinary incontinence. For inclusion, subjects must meet the inclusion criteria and must not meet the exclusion criteria. For more information about inclusion criteria, see Inclusion Criteria 3-3-2-2-1.

Patients with overactive bladder have a clinically and statistically significant lower quality of life, lower depression status, and poorer quality of sleep (35). Overactive bladder also causes additional health problems including increased risk of falls and fractures (presumably from nocturia in the elderly), urinary tract and skin infections, sleep disturbances and depression (36). Most studies about the cost of overactive bladder focus on the economic burden of overactive bladder, showing a total cost to the US healthcare system of $26.3B a year (37). Patients with refractory urgency urinary incontinence are those who are not achieving adequate control of incontinence symptoms through available modes of therapy. Such modes include behavioral therapy, pelvic floor exercises, and pharmacological therapy.

35. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P,Herzog AR, Corey R, Hunt TL and Wein AJ, Prevalence and burden of overactive bladder in the United States (NOBLE Study), World J Urol (2003) 20: 327–336.
36. Brown JS, McGhan WF, and Chokroverty S, Comorbidities Associated With Overactive Bladder, The American Journal of Managed Care, Vol. 6, No. 11, SUP (2000), S574-S579.
37. Wagner TH, Hu TW. Economic costs of urinary incontinence in 1995. Urology 1998;51:355-361.

3-7-3 Justification for Investigation

3-7-3-1 Potential Benefits of Treatment

According to the American Urological Association and its guideline for diagnosis and treatment of overactive bladder, the Panel interpreted the available percutaneous tibial nerve stimulation data to indicate that percutaneous tibial nerve stimulation can benefit a carefully selected group of patients characterized by moderately severe baseline incontinence and frequency and willingness to comply with regular return visits for administration of the percutaneous therapy. The Grade C evidence supports a potential benefit of tibial nerve stimulation in overactive bladder patients of improvements to incontinence episodes, voiding volume, quality of life, frequency, and nocturia. Furthermore, in a study by Finazzi-Agro et al., patients matching the population for the proposed study—females with detrusor overactivity incontinence—showed statistically and clinically significant improvements in mean incontinence episodes per 3 days, mean voids per day, mean voided volume, and mean QoL score (17). Thus, potential benefits of tibial nerve stimulation by eCoin include improvements to the number of incontinence episodes, voiding volume, frequency, and quality of life.

3-7-4 Additional Safety Profile Information

3-7-4-1 Description of Procedure

eCoin is placed into a subcutaneous pocket in the lower leg. The anatomical structures involved in the implantation procedure are skin, subcutaneous tissue and fascia. The

eCoin sits above the fascia so the deeper structures are not affected. Within the subcutaneous pocket, there are no significant nerves or vessels, other than subcutaneous veins which are of minimal significance. eCoin is placed about 3 mm above its target nerve (tibial nerve).

Similar to other inert prosthetic devices, a fibrous capsule is expected to form around the eCoin system. This capsule stabilizes the implant at its desired location and compartmentalizes it from the surrounding tissues (skin, subcutaneous fat and fascia).

3-7-4-2 Therapeutic or Stimulation Risks

Although stimulation could briefly exceed a comfortable level during the activation procedure, no serious complications from tibial nerve stimulation are known or anticipated. Stimulation pulses are charge balanced and at a charge density level known to be safe for neuromodulation with platinum electrodes (≤ 100 $\mu C/cm^2$). If stimulation intensity above the subject's comfort level is reached during programming in the clinic, the subject may feel discomfort or pain until the stimulation level is turned down. The subject may also experience a muscle twitch related to stimulation of the tibial nerve. Discomfort or muscle twitch is managed through optimal setting of stimulation amplitude to subject comfort levels. Adjustments to stimulation levels are only made in the clinic where the patient response can be monitored and adjustments made as needed.

Furthermore, the energy discharge of the eCoin battery is such that no harm will arise from heating due to a battery short. Direct shorting of the 120 mWh battery delivers less than 200 mW or 20 mW/cm^2 of heat from the device surface to tissue. This ensures a safe level of tissue heating (less than 2 degrees Centigrade) in a worst case direct short failure condition.

3-7-4-3 Risks of eCoin Implantation

The most probable risks associated with eCoin implantation include ecchymosis, erythema, and incisional pain at the implant site, intermittent paresthesias of the toes, foot, or lower leg, and other wound healing complications. Other risks are categorized as uncommon or rare and are reported below:

UNCOMMON (<5%)
- Hematoma at the incision site
- Implant site infection that leads to device explant
- Persistent implant site pain
- Severe pain during or shortly after the procedure
- Persistent wound healing complications lasting beyond 8 weeks post implant
- Persistent stimulation discomfort

RARE (<1%)
- Wound dehiscence
- Allergic reactions to local anesthesia
- Inflammation of nearby tendons
- Localized neuritis
- Surgical injury to adjacent nerves, vessels or tendons
- Allergic reaction to implanted materials
- Implant device failure leading to explant
- Implant device extrusion
- Implant device migration requiring explant or revision
- Implant device inversion

Device-related risks of the eCoin system can be deduced from the 50 year field of neuromodulation. The primary risks of importance are infection and lead-related problems (e.g. leadwire break, leadwire migration). For the leadless eCoin system, lead-related problems are not relevant. The rate of infection can be reasonably estimated based upon other neuromodulation devices, an implantable device whose implantation site is nearby that of eCoin, and the OUS clinical study. Infection can be mitigated through surgical training, adequate manufacturing controls, and adequate after-care instructions. Infection can be resolved through explantation of eCoin and/or antibiotics.

If needed, explantation of the eCoin device can be performed easily through simple opening of the capsule and removal of the device. If the capsule itself has a significant problem such as deep infection or dense scar tissue causing significant discomfort, then the capsule might require surgical excision, a procedure known as capsulectomy.

In the OUS clinical study of eCoin, the rate of patient infections requiring explantation was approximately 4.2%. See 2-2-2-1 for details.

The eCoin utilizes established biocompatible materials and manufacturing processes that are typical of implantable neurostimulators (titanium hermetic enclosure, silicone elastomer insulation coating (MED-4870) and with platinum stimulating electrodes).

3-7-5 Standards Conformance Demonstrating Safety

The eCoin system has been developed under design control in accordance with QSR 21 820.30 and ISO 13485.

3-7-5-1 Risk Management

Risk management conforms to ISO 14971:2012(E). A Risk Assessment has been completed for the SNS system based on Use, Design and Process FMEAs (See Risk Assessment Report 110-1493 in attachment 4-14).

3-7-5-2 Development Process and Design Verification Testing

Safety, Essential Performance, Design Verification and Marking have been completed per applicable parts of IEC 60601-1:2005+A1:2012(E) in compliance with active implantable medical devices ISO 14708-1:2000(E) and software life cycles per IEC 62304:2006. Attachment 4-16 is a summary of design verification testing results.

3-7-5-3 Biological Evaluation

The eCoin system is an active implantable device for long term patient contact duration (>30 days). The eCoin system has been subject to biocompatibility testing in accordance with the ISO 10993 series of standards. Biocompatibility compendiums were obtained from the suppliers of all materials to confirm that the supplier is also compliant with ISO 10993 requirements. The testing summarized in Table 3-2 was performed on sterile devices representing the final product using Good Laboratory Practices. Test Article Preparation was performed in accordance with ISO 10993-12. Based on the results of the in vitro testing, the eCoin Subcutaneous Neuromodulation System is safe and effective as an implant for the intended use.

Standard	Title	Result
ISO 10993-3:2003	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.	
	ISO Bacterial Mutagenicity Test – Ames Assay	Pass
	Mouse Lymphoma Assay	Pass

Standard	Title	Result
ISO 10993-5:2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity.	
	Cytotoxicity – Elution Test- MEM Extract	Pass
ISO 10993-6:2007	Subcutaneous Implantation Test – 90 days	Pass
	Systemic Toxicity Study of "SNS Biocompatibility Test Device" in Sprague Dawley Rats following Subcutaneous Implantation for 90 Days	Pass
ISO 10993-7:2008 /AC:2009	Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals.	Pass
ISO 10993-10:2010	Biological evaluation of medical devices - Part 10: Tests for irritation and delayed-type hypersensitivity.	
	Intracutaneous (Intradermal) Reactivity Test in New Zealand White Rabbits	Pass
	Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs	Pass
ISO 10993-11:2006	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity	
	Acute Systemic Toxicity Test in CD-1 Mice	Pass
	Pyrogen Test in New Zealand White Rabbits	Pass

Table 3-2: ISO 10993 Biocompatibility Testing

3-7-5-4 Sterilization and Sterile Packaging

The ethylene oxide sterilization process for the eCoin device was been developed, validated and is controlled per ISO 11135:2007 (see attachment 4-17). The sterile package sealing process and shelf life were developed and validated per ISO 11607 (see attachment 4-18).

3-8 *Description of the Device*

Valencia Technologies eCoin therapy for refractory urinary urge incontinence provides electrical stimulation to the tibial nerve from a small self-contained implant placed in the subcutaneous space over the tibial nerve in the lower leg. Subjects receive the implant unilaterally in a simple procedure under local anesthetic.

To stimulate the tibial nerve with the eCoin implant, the same parameters as previously demonstrated in animal and human studies are applied. The stimulation rate is 20 pulses per second (pps) at a pulse width of 0.2 ms. The stimulation pulse amplitude is adjusted to the highest comfortable level for the subject with an external controller. After activation, the implant automatically provides 30 minute stimulation sessions according to a fixed treatment interval schedule. In between sessions, the amplitude can be adjusted or automatic therapy can be turned off. The device contains a battery that will typically operate for 3 to 5 years before the device requires replacement.

3-8-1 Components

1) eCoin Implant – The implant is a coin-sized leadless battery powered device 23 mm in diameter and 2.2 mm thick. The electronics and battery are hermetically enclosed

in a titanium case. The materials in direct contact with tissue are the platinum electrodes, and the silicone elastomer jacket (NuSil MED 4870) that covers the titanium housing. Each implant receives a unique traceable serial number including labeling to place in recipient medical records.

2) External Controller – The external controller programs the device via a magnetic field using a custom access code secured wireless protocol.

3-8-2 Stimulation Settings/Parameters

Amplitude Range: 0.5 up to 15 mA (programmable)

Rate: 20 pulses per second (fixed)

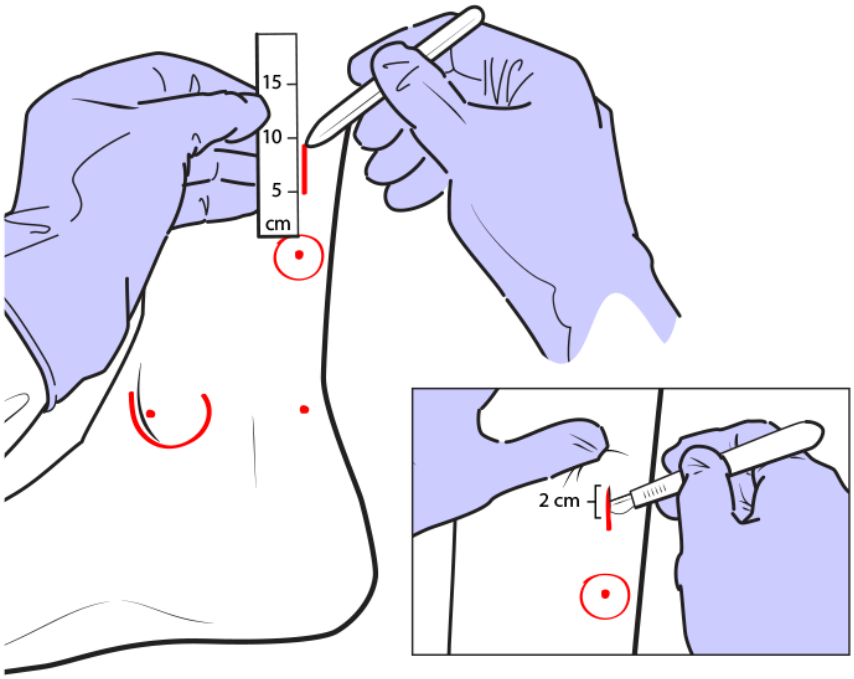
Pulse Width: 0.2 ms (fixed)

Treatment Duration: 30 Minutes (fixed)

Treatment Interval: 2 days for the first 12 weeks (42 sessions) and every 15 days thereafter (fixed)

3-8-3 Implant Procedure

Subcutaneous implantation of the eCoin is done under local anesthesia. The most prominent point of the medial malleolus will be palpated and marked. With the foot positioned at a 90-degree angle, a second marking is made 3 cm posterior to the medial malleolus marking. The implantation target location is found 3 cm cephalad to this second point along a line parallel to the posterior margin of the calcaneal tendon. Continuing on this line, the incision is made 3 cm cephalad to the target implantation site. The incision is made to the depth of the fascia with a width slightly smaller than that of the eCoin. Then, the eCoin is gripped with a surgical tool such as a needle driver or custom insertion tool, and slid on top of the fascia until it reaches the implantation site. The incision is then closed and dressed. See Attachment 4-2 for a complete surgical implant manual.



A. Marking the longitudinal incision line

B. Incision line should be 2 cm in length

3-8-4 Activation of eCoin System

After a 4 week period of implant healing, the eCoin devices are activated with the stimulation amplitude set to the subject's upper most comfortable level. Once activated, the eCoin applies a 30 minute session of neuromodulation therapy at the programmed amplitude every 2 days for a 12 week period and then every 15 days thereafter.

3-8-5 Subject Compliance Monitoring

eCoin Therapy: Neuromodulation therapy is provided automatically by the implant system and has no compliance requirements.

Drug Therapy: Subjects will be asked whether they are taking an overactive bladder medication through the primary endpoint to confirm that subjects are overactive bladder medication free.

Data: Compliance with voiding diaries is established through review by the clinical study coordinator at each center.

Appointment Compliance: Clinics' designated study coordinators will ensure subjects are compliant with study appointments within the scheduling parameters outlined in the Visit Overview described in Section 3-4-2.

3-8-6 Safety and Adverse Events

3-8-6-1 Medical Monitoring

The study will be approved by an independent ethical committee or institutional review board and subjects will be medically monitored by the participating Investigators.

3-8-6-2 Definitions of Adverse Events

Adverse Event (AE): Any untoward medical occurrence in a study participant whether or not there may be a causal relationship with this treatment / intervention. This can

include (but is not limited to) worsening of subject's overactive bladder condition and/or occurrence of serious sudden events.

System and Procedure Related Adverse Event: Any device or placement procedure related adverse event. This can include risks associated with the procedure, implant site or stimulation such as infection, or unexpected related adverse events that occur in relation to implant placement, median nerve stimulation or device failure. The Sponsor maintains a list of expected adverse events and is responsible for determining expectedness.

3-8-6-3 Classification of Events

3-8-6-3-1 *Relationship*

YES- related: The event has a reasonable possibility of a causal relationship to the administration of tibial nerve stimulation (procedure, device or stimulation) and no other etiology explains the event.

NO- not related: The event is independent of tibial nerve stimulation (procedure, device or stimulation) and/or the event appears to be explained by another etiology.

3-8-6-3-2 *Severity*

Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required and does not interfere with the subject's daily activities.

Moderate: Some limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.

Severe: Marked limitation in activity; interrupts participant's usual daily activity and may require medical intervention/therapy; hospitalization possible.

Serious: Results in death during the study period; is life-threatening; requires hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; results in a congenital anomaly or birth defect; requires medical or surgical intervention to preclude permanent impairment of a body function or to prevent permanent damage to a body structure, where the device is suspected to cause such intervention; other important medical events not captured by the other categories where the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes.

3-8-6-3-3 *Expectedness*

Expected: Any adverse reaction whose nature and intensity are consistent with that described under risk assessment.

Unexpected: Any adverse reaction not included under risk assessment.

3-8-6-4 Recording of Adverse Events

Expected device related AEs will be recorded on case report forms in Attachment 4-9, which are used at each visit. Unexpected or unrelated AEs or any requiring medical attention will be checked on CRFs and further recorded on AE forms. Subjects will be requested to report adverse urologic events that are inconsistent with their normal medical condition that occur in between visits to the study coordinator or medical staff who will record on AE forms. All adverse events will need to be evaluated and assigned

by a medical reviewer on or designated by the Data and Safety Monitoring Board (DSMB) with regards to:

1) Relatedness or causality to the study device
2) Severity
3) Expectedness
4) Action taken

The Sponsor is responsible for determining if an adverse event is unexpected. If expectedness is assessed by a medical reviewer as unexpected, the Sponsor will be notified and will evaluate and assign a final determination that may or may not result in reporting requirements.

At each contact with the subject, the Investigator will obtain information on AEs by specific questioning and examination. In the CRF for visits, if an event is reported, the AE checkbox will be selected. This selection will trigger a separate form to be filled out which records the following information:

1. Subject Number
2. Adverse Event (AE)
3. Date of AE onset
4. Date of AE cessation
5. Severity
6. Expectedness
7. Causality
8. Was the patient hospitalized? If yes, provide dates.
9. Will the patient continue with treatment, and will any be missed?
10. Did the patient add or change any other associated medication and what were the changes/additions?
11. Was there any other action taken?

When an AE has been recorded, the PI or sub-PI for the study must sign and approve the assessment on the Sponsor provided form. The Study monitor will keep track of the reported AEs. A sample of the AE report form is in Attachment 4-9.

3-8-6-5 Reporting Procedures

For Serious Adverse Events (SAEs) or suspected Unanticipated Adverse Device Effects (UADEs), the Study Coordinator, the PI and the Sponsor will be alerted. The timeline for medical review and assessment is 24 hours for SAEs and 7 days from subject reporting of non-Serious unexpected device related AEs. For suspected UADEs the Sponsor will promptly provide an expectedness determination. The Investigator must promptly inform the Ethics Board or IRB of SAEs or determined UADEs per local reporting requirements.

The SAE form provided by the Sponsor should be completed and signed by the Investigator or physician sub-investigator and faxed or emailed to the Sponsor per the instructions on the form. The entire SAE form needs to be completed, if possible, to make available in a timely manner complete relevant information thus limiting requests for additional information. Each SAE reported on an SAE form must also be reported in the adverse event section of the CRF.

These events will be reported by the Sponsor as appropriate to the regulatory authorities according to relevant jurisdictional medical device regulations. The Investigator will receive notification of these events across all study centers from the Sponsor.

3-8-6-6 Adverse Event Reporting Period

Adverse event information will be collected during the study duration - between Informed Consent and final follow-up. If the patient presents to the Investigator after the study period and a device related AE is suspected, it should be reported to the Sponsor using the post study AE form provided by the Sponsor. Post-study adverse events should be reported to the Sponsor after the study period if they are:

1) AEs that are device related resulting in a reprogramming, revision surgery or explant (explant for reasons other than for normal end of life – e.g. battery depletion) for which the patient presents to the PI.
2) AEs that occur during or related to an explant procedure performed at the normal device end of life.

3-8-7 Subject Withdrawal & Termination

3-8-7-1 Early Withdrawal of Subjects

Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits or become lost to follow-up for any reason. The devices must be recommended to be explanted if they are withdrawn.

3-8-7-2 Terminating Subject Participation

A subject's continued participation in the study must be terminated for the following reasons:

1) In the Investigator's opinion, continued participation would be detrimental to the subject's well-being.
2) Subject is noncompliant with the protocol.
3) Subject is lost to follow up (after 5 failed attempts to contact).
4) Subject becomes pregnant during the trial.
5) Subject uses prohibited treatments, medication changes, or procedures as defined in the exclusion criteria.

The subject's eCoin system must be recommended to be explanted if subject participation is terminated.

3-8-7-3 Withdrawal/Termination Procedures

If premature withdrawal occurs for any reason, the Investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the Case Report Form for reporting to the Sponsor.

Subjects enrolled in the study will not be replaced if they withdraw or are terminated from the study after device activation. Provisions for device explantation will be arranged.

3-8-7-4 Early Study Termination

The study can be terminated at any time for any reason by Valencia Technologies. Should this be necessary, the subjects should be seen as soon as possible and treated as described in the early withdrawal section for a prematurely withdrawn subject. The Investigator may be informed of additional procedures to be followed in order to ensure

that adequate consideration is given to the protection of the subjects' interests. The Investigator will be responsible for informing the IRB of the early termination of the trial. If required, provisions for the explant of the eCoin system will be arranged.

3-8-7-5 Data Collection and Follow-up for Withdrawn Subjects

Subjects will not be followed after completion of or withdrawal from the study.

3-8-8 Data and Safety Monitoring Board

A Data and Safety Monitoring Board of at least three members will review data including a monthly report of Adverse Events and data analyses at 1 months post implantation (a primary safety endpoint) and 3 months post activation (primary safety and efficacy endpoint). This DSMB will meet telephonically at least monthly until the study reaches the primary endpoint to review aggregate and individual subject data related to safety, data integrity and overall conduct of the trial. They will be responsible for the review of safety endpoints. The DSMB will provide recommendations to continue or terminate the trial depending upon this review. A DSMB charter is set forth in a DSMB Charter document (see 4-10).

3-9 *Data Analysis Plan*

3-9-1 Data Collection

All study data will be recorded onto Case Report Forms (CRFs) provided by Valencia Technologies. All CRFs will be completed using de-identified data.

CRF completion may be delegated to other study personnel but the Investigator remains responsible for the accuracy and integrity of all data entered on CRFs. CRFs will be completed and sent to the designated representative for Valencia Technologies as directed, in an expedited fashion. All CRFs will be completed by study personnel only. Valencia or its designee will work with participating sites to secure data clarification and to obtain additional relevant medical documentation on participants enrolled into this trial.

CRF's for the study include:

1) Screening
2) Baseline
3) Implantation
4) Implant Healing Check
5) eCoin Activation
6) Safety Follow Up (1 month post-activation)
7) Follow Up (2, 3, 4, 6 months post-activation) and long term monitoring (12 months post-activation)
8) Adverse Event
9) Study Termination

3-9-2 Interim Monitoring

All clinical sites will be monitored periodically by Valencia Technologies or its designated representatives. Telephone contacts and site visits will be made throughout the course of the study.

During site visits, the monitor will review participant records, device accountability and storage, general study procedures, and will discuss any problems with the Investigator. Monitors will audit data collected on CRFs and verify it against source documentation in accordance with the Clinical Monitoring Plan in Attachment 4.22. Monitors will confirm that written Informed Consent was properly obtained prior to enrollment of all participants. Any evident pattern of non-compliance will be addressed with the Investigator. If appropriate corrective actions are not subsequently undertaken, Valencia reserves the right to suspend enrollment at the site and/or withdraw the site from the study.

At the close of the study at a research site, the clinical monitor will make a final on-site visit. The purpose of this visit is to collect all outstanding study data documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies

shipped to the Investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

3-9-3 Analysis Plan Summary

This is a single-arm, prospective trial designed to demonstrate the safety and effectiveness of the eCoin tibial nerve neuromodulation system for the treatment of refractory urinary urge incontinence. A total of 50 subjects from about three to five different centers in New Zealand and the United States will be implanted with eCoin in the single arm study. Up to 35 subjects from the United States will be implanted with eCoin.

3-9-3-1 Primary Endpoint

The primary endpoint of this study is the change in number of incontinence episodes from baseline to three months post-activation.

Key Secondary Endpoints

The key secondary endpoint is the percentage of responders in subjects implanted with the device. Responders are defined as subjects with a 50% or greater reduction in urge incontinence episodes from baseline to three months post-activation.

3-9-3-2 Exploratory Secondary Endpoints

Estimate the difference in change from baseline in number of incontinence episodes at three and four months post-activation in all responder subjects with data available at three and four month visits.

Estimate the change, expressed as a percentage from baseline, in incontinence episodes from baseline to three months post-activation in responder subjects.

Estimate the change in number of micturitions from baseline to three months post-activation in responder subjects.

Estimate the change in mean voided volume from baseline to three months post-activation in responder subjects.

Estimate the change in I-QoL scores from baseline to three months post-activation in responder subjects.

Patient satisfaction measured at 3 months post-activation.

3-9-4 Primary Hypotheses

The goal is to show the size of the treatment effect (reduction in leakage episodes) in responder subjects after three months of eCoin therapy. The null hypothesis is that there is no reduction in the mean number of leakage episodes from baseline after 3 months of therapy.

The primary effectiveness hypotheses being tested is:

H0: $\mu(\text{Subject}) \leq \mu(\text{Subject Baseline})$ **vs.** **H1:** $\mu(\text{Subject}) > \mu(\text{Subject Baseline})$

Where $\mu(\text{Subject})$ and $\mu(\text{Subject Baseline})$ are the mean number of leakage episodes at three months post-activation and at baseline. Rejection of the null hypothesis at a two-sided significance level of 0.05 indicates a mean reduction greater than zero.

3-9-5 Sample Size Calculation

The sample size for this study is based on achieving adequate power to detect the size of the effect at 3 months post-activation. The response variable is the change from baseline in the number of urge incontinent episodes after 3 months of therapy (3 months post-activation). For the primary endpoint, urge incontinent episodes are measured prospectively using 3-day voiding diaries administered at baseline and 3 months post-activation. Subjects are required to have at least three urge incontinence episodes over 24 hours on a three-day voiding diary at baseline. A sample size of 25 subjects provides 80% power to detect a true difference of 0.63 leaks per day, assuming the standard deviation in the in the response variable is 1 leak per day with a two-sided 0.05 significance level. The sample size assumes a 10% loss to follow-up over the 3-months of treatment.

3-9-6 Analysis Sets

Efficacy analyses will be generated for the ITT, PP and Responder analysis sets, with the analysis on the Responder set being the primary analysis. Safety analysis will be performed on the safety analysis set.

1) Responder: The subset of PP who achieve at least a 50% reduction in leakage episodes from baseline.
2) Safety: All subjects implanted with the device.
3) Intent-to-Treat (ITT): All enrolled subjects meeting the inclusion criteria of the study who are not ineligible because of exclusion criteria; this is a secondary analysis population for the efficacy endpoints and a primary analysis population for the safety endpoints. Missing outcome data will be handled per 3-9-9.
4) Per-Protocol (PP): The subset of ITT subjects who complete the 3 month post activation follow-up period.

3-9-7 Exploratory Subgroup Analyses

Subjects who respond to treatment (i.e. who achieve at least a 50% reduction in number of leaks from baseline to three months post-activation) will be compared to non-responders in terms of baseline characteristics and demographics as described in the statistical analysis plan. Efficacy endpoints will be analyzed for the responder subset.

3-9-8 Calculation of Efficacy Variables

Change in Incontinent Episodes: Incontinent episodes (IE) are measured prospectively using 3-day voiding diaries administered at baseline, 1, 2, 3, 4, and 6 months post-activation of the eCoin system.

Change in Severity and Frequency of Leakage: Severity and frequency of leakage is measured prospectively using 3-day voiding diaries administered at baseline, 1, 2, 3, 4, and 6 months post-activation of the eCoin system.

Change in Frequency: Frequency of urination is measured prospectively using 3-day voiding diaries administered at baseline, 1, 2, 3, 4, and 6 months post-activation of the eCoin system.

Change in Voided Volume: Voided volume is measured prospectively using a urine collection tool and captured using 3-day voiding diaries administered at baseline, 1, 2, 3, 4, and 6 months post-activation of the eCoin system.

Change in Quality of Life: Quality of life is measured prospectively using the I-QoL questionnaires administered at baseline, 1, 2, 3, 4, and 6 months post-activation of the eCoin system.

Patient Global Impression of Improvement: The level of patient satisfaction with the eCoin neuromodulation system will be rated by the subject on a descriptive scale of very much worse, much worse, worse, about the same, better, much better, and very much better.

Patient Reported Satisfaction: The level of patient satisfaction with the eCoin neuromodulation system will be rated by the subject on a scale of 1 to 5 where 1 is Not at All Satisfied, 2 is Slightly Satisfied, 3 is Somewhat Satisfied, 4 is Very Satisfied and 5 is Completely Satisfied.

3-9-9 Missing Outcome Data

Due to device implantation, few patient drop-outs are expected through primary and secondary endpoints. Careful clinical planning that minimizes patient dropouts will be implemented.

Multiple imputation per the statistical analysis plan will be used for missing data.

3-9-10 Safety Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The terms included in the tabulations will be organ system and preferred terms. Tabulations of general AEs will be provided by treatment group by time point, and will include the number of subjects exposed, the number of subjects with at least one AE, and the number of subjects with at least one AE by organ system and preferred term. These tabulations will be repeated for all AEs recorded as having a causal relationship to investigational product. Tabulations of local AEs will be provided at 1 and 3 months, and will include the number of subjects exposed, the number of subjects with at least one AE, and the number of subjects with at least one AE by preferred term. Separate tables will be provided, if relevant, for SAEs or events leading to withdrawal from study.

3-10 *Data Handling, Record Keeping and Study Monitoring*

3-10-1 Confidentiality and Security

The Investigator will ensure that the subject's confidentiality is maintained on the CRFs or other documents submitted to the Sponsor. Subjects should be identified by their initials and a subject study number only. Documents that are not for submission to the Sponsor such as the signed informed consent forms should be kept in strict confidence by the Investigator. In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The Investigator will inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject. Information about study subjects will be kept confidential and managed according to the requirements of the clinical sites regulatory authority. As a part of the consent process, subjects will sign an authorization informing the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- What rights does a research subject have to revoke their authorization for use of their PHI

3-10-2 Training

All study forms and procedures will be reviewed with medical/study staff at the participating centers. Investigators or surgical designee will also be medically trained and certified by the Sponsor to perform the implant procedure. Training will include any combination of cadaver training, video, or supervised procedures. To perform the procedure the Investigator or designated medical doctor will need to be experienced in urology or uro-gynecology, and be certified by the Sponsor.

3-10-3 Documentation, Case Report Forms and Source Documents

All documents will be signed off by the Sponsor and controlled such that any revisions are approved and tracked, with each document identified with a document number and revision code. Investigators will maintain the following items of documentation in the **Investigator's Study File on site:**

- Protocol and any amendments
- Consent forms (sample, and subject signed and dated)
- IRB/ERC approval for the protocol and consent form
- Agreement letter sent to Sponsor
- Case Report Forms
- Adverse event or Problem reports to Sponsor and IRB
- Inventory control log
- Enrollment Log
- Records of deviations, violations, and amendments
- Implant Registration Cards, where required by local regulations

Case Report Forms: All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not

completed or the question was not asked, select “N/D”. If the item is not applicable to the individual case, select “N/A”. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. Case Report Forms will be kept in the Study File.

Source Documents: medical records, voiding diaries, QoL questionnaires, etc. will be maintained at the study clinic.

3-10-4 Device Accountability

Each device has a unique serial number assigned. In the device box, there will be 2 adhesive labels with the serial number of the device. At the time of implantation, one sticker will be placed on the Implantation CRF and another sticker will be placed on the patient implantation card (see 4-7). The Sponsor is responsible for managing the device accountability log across the study. Each site will have a device tracker to be reconciled at the conclusion of the study.

3-10-5 Monitoring Procedures, Auditing, and Inspecting

A clinical research monitor will supervise conduct of the study at each site in accordance with the Clinical Monitoring Plan provided in Attachment 4-22. The monitor will visit the Investigator and the study facility at periodic intervals in addition to maintaining ongoing telephone, e-mail, and letter contact. The monitor will maintain up-to-date personal knowledge of the study through observation, review of study records and source documentation, and discussion of the study with the Investigator and study personnel. The study site will assist the monitor by providing access to all relevant study materials.

The clinical monitors will be qualified members of the Clinical Research Department of Valencia Technologies who have been trained on the study protocol, monitoring procedures, and standard operating procedures based on Good Clinical Practice and other applicable Federal regulations.

The monitor’s responsibilities are:

- Conduct Site Initiation visit (after IRB approval/before first subject enrollment).
- Conduct periodic monitoring visits.
- Compare case report forms to source documents.
- Review Investigator’s files for accuracy, currency, and completeness.
- Ensure that informed consents are obtained.
- Ensure that IRB review is current.
- Ensure protocol compliance, document deviations.
- Prepare reports of visits.
- Ensure adverse events are reported.
- Conduct closeout visit (after all case report forms are received in house).

3-10-6 Protocol Deviations and Compliance

3-10-6-1 Major Protocol Deviations

A major protocol deviation is defined as one that affects the safety of the subject or the scientific validity of the results.

1) A Physician Investigator can deviate from the protocol in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant. The Sponsor and the IRB/Ethics Committee must be notified as soon as possible, but not later than 5 days after the emergency situation occurred.

2) Any non-emergency, major deviation to the protocol must be approved by the Sponsor and the IRB/Ethics Committee prior to implementation. If a major deviation occurs that is not in response to the protection of a subject, without prior approval, the event is considered non-compliance. Non-compliance must be reported to the IRB/Ethics Committee promptly – no later than 5 days after the deviation. A PI's failure to report promptly any major deviation for which the PI did not obtain prior approval is itself an incident of non-compliance and will be evaluated by the Sponsor and could be grounds for physician disqualification.

3-10-6-2 Minor or Administrative Protocol Deviations

A minor deviation is defined as one that does not affect the safety of the subject or the scientific validity of the results. If a minor deviation from the protocol is discovered, it should be noted on the protocol deviation log at the site and brought to the attention of the monitor at the next CRA visit. These deviations do not need to be reported to the IRB/Ethics Committee. Examples of a minor protocol deviation:

1) Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule.
2) Study procedure conducted out of timeframe, e.g. 3-day diary
3) Participant failure to initial every page of the consent form
4) Participant failure to return patient diary
5) Copy of the ICF not given to the participant
6) Missing original signed consent, but a copy exists
7) Patient not given implant card

3-10-6-3 Analyzing Deviations

At each monitoring visit, the deviations log will be analyzed along with any additional deviations that might be discovered during the monitoring visit. If any of the minor deviations are deemed to have an impact on the trial outcomes, this issue must be brought to the attention of the Sponsor.

3-10-6-4 Statement of Clinical Compliance

The study will be conducted in accordance with the design and specific provisions of this IRB/Ethics Committee approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s). The Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB/Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants. The Investigator will promptly report to the IRB/Ethics Committee and the Sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

3-11 *Methods, Facilities, and Control Information*

3-11-1 Device Manufacturer

3-11-1-1 Manufacturer name, address and contact information

Name of device manufacturer: Valencia Technologies Corporation
Address: 28464 Westinghouse Place, Valencia, CA 91355
Contact Person: Dave Peterson, Chief Technology Officer
Telephone Number: (661) 775-1414
Fax Number: (661) 775-1411

3-11-1-2 Manufacturer compliance with Subpart C, Design Controls (section 820.30), the Quality System Regulations (21 CFR Part 820)

The eCoin Subcutaneous Neuromodulation System is manufactured by Valencia Technologies Corporation under design controls per QSR 21 820.30 and ISO 13485.

3-11-1-3 Device Design and Manufacturing Information

3-11-1-3-1 Device Design

Engineering drawings of the eCoin Subcutaneous Neuromodulation System described in section 3-8 are in attachment 4-19. Materials used outside of the hermetic package in the eCoin device are in attachment 4-20.

Design inputs for the eCoin Subcutaneous Neuromodulation System include the requirements for functional performance and safety including applicable regulatory and legal requirements as well as the outputs of risk management. The design outputs for the eCoin Subcutaneous Neuromodulation System are captured in functional specification requirements. These design outputs are verified in the testing summarized in attachment 4-16 using test articles that are representative of the final product. The clinical use of the eCoin device has been validated in a successful first in human feasibility trial from 2013 through 2016 for the treatment of drug resistant hypertension in adults per the protocol in attachment 4-11.

Design Reviews are conducted with representatives of functions concerned with the design and development stage being reviewed. Other specialist personnel are included as needed. Design changes arising from these reviews are verified and validated before approval and release.

3-11-1-4 Manufacturing Controls

Assembly procedures with test procedures are in place to ensure the eCoin device is produced in accordance with the design and performance specifications (attachment 4-23). Each device is tracked individually by serial number with traceability to components and all production steps maintained in a device history record.

3-11-1-5 Processing, Packaging, Storage

The procedures for sterile packaging, sterilization and storage are in attachment 4-24.

3-12 *Study Sites and Investigators*

3-12-1 Organization and Participating Center

3-12-1-1 Principal Investigators

All U.S. based Principal Investigators participating in the study will have signed an Investigator Agreement, a template of which is enclosed as Attachment 4-21 in compliance with § 812.43. New U.S. based Principal Investigators will be required to sign the Investigator Agreement before being added to the study. Attachment 4-25 is the list of investigators.

Sponsor

Valencia Technologies Corporation
Stacy Chambliss, Tel: +1 (661)775-1414 ext. 1002
28464 Westinghouse Place
Valencia CA, 91355
United States

3-12-2 Funding Source and Conflicts of Interest

The study is funded by Valencia Technologies and participating centers will be paid according to clinical trial agreements. No participating physicians are otherwise involved or have any ownership in the company.

3-12-3 Institutional Review Board / Ethics Committees

Institutional Review Board / Ethics Committees will approve the protocol for each respective center pursuant to center requirements or under an independent review board.

3-12-4 Roles and Responsibilities

3-12-4-1 Investigator

The following are the responsibilities of the Investigator:

1) Assure IRB/Ethics Committee approval of protocol and informed consent is obtained.
2) Follow the study protocol.
3) Permit monitor to inspect facilities and records.
4) Permit regulatory inspections of facilities and records, if necessary.
5) Inform a patient of any risks and benefits associated with use of the device, and obtain the patient's written consent for its use.
6) Enroll subjects, execute study, transcribe data from source documents to Case Report Forms.
7) Submit annual progress reports, final reports, and adverse event reports to IRB/Ethics Committee and to Sponsor.
8) Return unused study articles, record their receipt, disposition, and return
9) Refrain from promoting study or study articles in any manner that is not Sponsor authorized.
10) Conduct study in accordance with the protocol.
11) Track Sponsor provided inventory and assignments
12) Maintain medical histories of subjects.
13) Retain records for 10 years or as required by law following completion of the study.

3-12-4-2 IRB/Ethics Committee

The following are the responsibilities of the IRB or Ethics Committee, where one group will be designated by the center to perform the function:

1) Review and approve, modify, or disapprove the study protocol and informed consent form.
2) Receive continuing and final reports on study progress.

3-12-4-3 Sponsor

The following are the responsibilities of the Sponsor:

1) Submit protocol and informed consent to IRB/Ethics Committee and FDA and await approval.
2) Submit proposed amendments to the protocol and informed consent to IRB/Ethics Committee and Regulatory Authority (where applicable and await approval, unless the change reduces the risk to subjects).
3) Assure IRB/Ethics Committee and Regulatory Approval (where applicable) is obtained.
4) Select and train monitors.
5) Select and train Investigators and study personnel.
6) Obtain agreement letter and c.v. of Investigator(s).
7) Control shipment of test and control articles.
8) Conduct overall administration of study.
9) Investigate unanticipated, device-related adverse events.
10) Document protocol deviations and violations.
11) Report and respond to the DSMB.

3-12-5 Subject Compensation

Subjects will not be paid for participation in this study. However they will be provided a small stipend for travel and accommodation expenses associated with the study treatment and follow-up requirements.

3-13 *Study Timetable*

Study initiation is planned for April 2017. Study enrollment of 100 subjects (to implant 50 subjects) is expected to be completed by July 2017. Study endpoints are expected to be reached for all subjects by end of November 2017. Monitoring is expected to be completed in August 2018.

4 Attachments

4-1 *3-day Voiding Diary*

4-2 *Manuals, and Labels*

4-3 *Investigator's Brochure*

4-4 *Patient Trial Brochure*

4-5 *Informed Consent Document*

4-6 *Patient Global Impression of Improvement*

4-7 *Patient Implantation Card*

4-8 *Case Report Forms*

4-9 *Adverse Event Form*

4-10 *DSMB Charter*

4-11 *OUS Study for Hypertension Protocol*

4-12 *OUS Study for Hypertension CRFs for Infections*

4-13 *OUS Study for Hypertension DSMB Letter Recommending Suspension of Implantation at Site 12*

4-14 *SNS Risk Assessment (110-1493)*

4-15 *Summary of Risks and Mitigations*

4-16 *Design Verification and Validation Reports*

4-17 *Ethylene Oxide Sterilization Validation Reports*

4-18 *Sterile Packaging Validation Report*

4-19 *Engineering Drawings*

4-20 *eCoin Device Materials*

4-21 *Template Investigator Agreement*

4-22 *Clinical Monitoring Plan*

4-23 *Assembly Procedure eCoin Device*

4-24 *Assembly Procedure Sterilization and Packaging Clinical Monitoring Plan*

4-25 *List of Investigators*

4-26 ***303-1122 Software Design Specification SNS***

4-27 *Biocompatibility Reports*