Rev	Description	ECO #	Date	Originator
1	Initial Release.	143449	08/16/23	C. Mazzola

Evaluating **E**ffectiveness of **S**ensory and **S**ubsensory Stimulation Amplitudes with **e**Coin® Tibial **N**erve Stimulation in Urgency Urinary In**C**ontinence **E**pisodes and **E**pisodes and Quality of Life (ESSENCE)

Statistical Analysis Plan
Version 1.0
June 16, 2023

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Synopsis

Protocol title	Evaluating Effectiveness of Sensory and Subsensory Stimulation Amplitudes with eCoin® Tibial Nerve Stimulation in Urgency Urinary InContinence Episodes and Quality of Life (ESSENCE)
Treatment assignment	Enrolled subjects will be assigned to the following treatments: • eCoin programmed at sensory level • eCoin programmed at subsensory level
Study design	Prospective, multi-center, double-blinded randomized controlled clinical trial designed to observe the effectiveness and QOL of two different programming methods for the FDA-approved eCoin device.
Analysis population	The primary analysis population for the effectiveness outcomes will be the per protocol population. The safety analyses will be the safety population: all enrolled subjects who undergo a procedure for implantation of eCoin.
Primary efficacy outcome	The primary endpoint is to explore the effect of two different eCoin programming methodologies on the reduction of UUI episodes per day on a 3-day voiding diary after 3 months of eCoin tibial nerve stimulation.
Key (alpha-preserved) secondary efficacy outcome	The secondary endpoints are: 1. Change from baseline in the patient reported quality of life as assessed by the Health-Related Quality of Life (HRQL) portion of the Overactive Bladder questionnaire (OABq) survey after 2, 3, and 4 months of therapy at two different programming methodologies. 2. Reduction from baseline in the number of urgency urinary incontinence episodes per day on a 3-day voiding diary (72 hours) after 2 and 4 months of eCoin tibial nerve stimulation at two different programming methodologies. 3. Improvement from baseline of patient satisfaction with UUI symptoms as gathered from patient satisfaction surveys after 2, 3 and 4 months of therapy at two different programming methodologies.
Primary safety outcome	Safety will be assessed by collection of adverse events related to the device and/or procedure, all serious adverse events, and device malfunctions.
Statistical method for primary efficacy analysis	The primary efficacy outcome will be based on the per protocol population. The reduction from baseline in the number of UUI episodes per day on a 3-day voiding diary (72 hours) after 3 months of eCoin device tibial nerve stimulation will be summarized with descriptive statistics. The mean reduction of UUI episodes per day along with its two-sided 95% confidence interval will be summarized for subjects in both arms and by all subjects. The primary endpoint is exploratory in nature. There are no pass/fail

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	criteria to define the study success and there is no powered comparison between the two treatment arms
Sensitivity analyses	Efficacy analysis will also be performed on the ITT population.

Abbreviations and Definitions

AE	Adverse Event
CRF	Case Report Form
HRQL	Health-Related Quality of Life
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
OAB	Overactive Bladder
OABq	Overactive Bladder Symptom Quality of Life Questionnaire
PP	Per Protocol
PT	Preferred Term
PVR	Post void residual
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
UUI	Urgency Urinary Incontinence

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Contents

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1. Introduction

This statistical analysis plan (SAP), which is based on the ESSENCE study protocol, defines the methods that Valencia Technologies Corporation (Valencia) plans to use to analyze the data from the ESSENCE study. If the protocol is amended, the SAP may be amended as well. If there are minor discrepancies between the analysis described in the protocol compared to the SAP, the SAP will serve as the primary source. The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced are appropriate to explore the study objectives.

2. Responsibilities

The Valencia technologies biostatistician will perform the statistical analysis and is responsible for the production and quality control of all tables, figures, and listings.

3. Scope of Analysis

The analysis described in this SAP will explore the efficacy and safety of the eCoin Tibial Nerve stimulator programmed at sensory and subsensory amplitude settings.

4. Study Objectives and Endpoints

4.1. Study Objectives

The ESSENCE study is designed to explore the effectiveness of the eCoin System programmed at two different programming methodologies (sensory, subsensory) for the treatment of urgency urinary incontinence (UUI) by assessing the improvement in urinary incontinence episodes on a 3-day voiding diary.

Additionally, this study is designed to assess the improvement in the patient reported quality of life utilizing the Health-Related Quality of Life (HRQL) section of the Overactive Bladder Symptom Quality of Life Questionnaire (OABq) and patient satisfaction surveys at two different programming methodologies.

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4.2. Study Endpoints

The primary endpoints and secondary endpoints are listed in Table 1 below.

Table 1. Endpoints

Primary Endpoint The primary endpoint is to explore the effect of two different eCoin programming methodologies on the reduction of UUI episodes per day on a 3-day voiding diary after 3 months of eCoin tibial nerve stimulation.
Secondary Endpoints 1. Change from baseline in the patient reported quality of life as assessed by the Health Related Quality of Life (HRQL) portion of the Overactive Bladder questionnaire (OABq) survey after 2, 3, and 4 months of therapy at two different programming methodologies. 2. Reduction from baseline in the number of urgency urinary incontinence episodes per day on a 3-day voiding diary (72 hours) after 2 and 4 months of eCoin tibial nerve stimulation at two different programming methodologies. 3. Improvement from baseline of patient satisfaction with UUI symptoms as gathered from patient satisfaction surveys after 2, 3 and 4 months of therapy at two different programming methodologies.

5. Study Methods

5.1. Study Design

The ESSENCE study is a double blind, randomized controlled, prospective, multicenter study designed to explore the effectiveness of eCoin tibial nerve stimulation programmed at different sensory levels. Enrolled subjects who meet all eligibility criteria and are implanted with the device will be randomized into one of two groups assigned to a parallel assignment intervention model. The two groups are: an arm where subjects are programmed at sensory level and an arm where subjects are programmed at a subsensory level. Blinding will be maintained for both the investigator and patient through 3 months post-activation of eCoin.

Participating sites will enroll patients that experience Urge Urinary Incontinence (UUI) and collect de-identified subject data via paper Case Report Forms (CRFs).

The purpose of this study is to explore the effect of two different amplitude settings on the reduction of UUI episodes per day as compared to baseline. The objectives are descriptive in nature and there is no powered comparison between the two treatment arms.

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5.2. Patient Selection

Subjects who have signed informed consent may be scheduled for a screening visit to determine eligibility. During the screening visit, the inclusion/exclusion criteria will be assessed, and the patient's medical records reviewed. Additionally, the investigator will perform a physical exam and evaluate whether the patient's general health is sufficient to participate in the study. Subjects that meet all of the inclusion criteria and none of the exclusion criteria may be enrolled in the study.

5.2.1. Eligibility Criteria

Inclusion Criteria

- Women and men above 18 years old or older at time of consent
- Individual with diagnosis of overactive bladder with urgency urinary incontinence.
- Individual has at least one urgency urinary incontinence episode on each of three days as determined on a 3-day voiding diary.
- Individual understood the nature of the procedure and study requirements and provided written informed consent.
- Individual is willing to comply with specified protocol requirements and follow-up evaluations.
- Individual is without pharmacological treatment of overactive bladder (anticholinergic and β3-adrenoceptor agonists) for 2 weeks prior to baseline.
- Individual is intolerant of or has an inadequate response to any of anticholinergics, β3-adrenoceptor agonists, onabotulinumtoxinA, or who have undergone percutaneous tibial nerve stimulation (PTNS).
- Individual is determined to be a suitable surgical candidate by physician.

Exclusion Criteria

- Individual is not appropriate for eCoin therapy based upon the US FDA-approved IFU requirements.
- Individual has predominantly stress urinary incontinence (greater than 1/3 of leaks on baseline diary are stress).
- Individual has clinically significant bladder outlet obstruction.
- Individual has an active urinary tract infection at time of enrollment.
- Individual has had four or more symptomatic UTI's in the last 12 months.
- Individual has microscopic hematuria that has not been evaluated.
- Individual has significant lower urinary tract pain or has been diagnosed with interstitial cystitis or bladder pain syndrome that is actively being managed.
- Individual has post void residual greater than 200 cc.
- Individual has an active diagnosis of bladder, urethral, or prostate cancer.
- Individual has had a prior anti-stress incontinence surgery within the last year.

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- Individual is pregnant, breast feeding, is less than 12 months post-partum or intends to become pregnant during the study.
- Individual has uncontrolled diabetes mellitus (Hemoglobin A1C>7).
- Individual has an implantable pacemaker or implantable cardiac defibrillator (ICD).
- Individual has been treated with onabotulinumtoxinA in the previous 9 months prior to enrollment.
- Individual has been treated with percutaneous tibial nerve stimulation (PTNS) within the previous 4 weeks prior to enrollment.
- Individual has a clotting or bleeding disorder or is unable to hold anticoagulant therapy for the implant procedure at the discretion of the investigator.
- Individual is neutropenic or immune-compromised.
- Individual has lower extremity pathology such as:
    a. Previous surgery and/or significant scarring at the planned implant location
    b. Ongoing dermatologic condition at the implant site, including but not limited to dermatitis and autoimmune disorders
    c. Clinically significant peripheral neuropathy in the lower extremities
    d. Pitting edema at the implant location (≥ 2+ is excluded)
    e. Inadequate skin integrity or any evidence of an infection or inflammation in either lower leg
    f. Moderate to severe varicose veins
    g. Open wounds or recent trauma
    h. Arterial and/or vasculitis disease in the lower extremities
    i. Chronic venous insufficiency with a history of skin change (hyperpigmentation, lipodermatosclerosis, ulceration) in the ankle region
- Individual has neurogenic bladder dysfunction.
- Any condition that, in the investigator's opinion, would preclude participation in the study (e.g., comorbidity that places subject at increased risk for surgical intervention, medical condition that may increase the risk associated with study participation or may interfere with interpretation of study results, inability to adhere to the visit schedule)

5.3. Randomization and Blinding

Randomization assignments will be generated by the software program Sealed Envelope Ltd. 2022 using block randomization with variable block sizes of 2, 4, and 6. No stratification will be used. Randomization assignments will be generated for 50 subjects. After production of the allocation sequence, the sequence will be locked, password protected and placed in an online file storage system by the Clinical Trial Manager or staff who produced it. The Investigator and Patient must not view the randomization sequence prior to unblinding, unless there are extenuating circumstances described below.

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Both the principal investigator (including site study staff) and patient will be blinded to the patient's treatment assignment until completion of the primary endpoint visit at 3 months post-activation. The FCE will be unblinded to the participant's treatment assignment, allowing them to activate the patient to their treatment level. The blinding technique is described in detail in the ESSENCE Blinding Work Procedure document.

Treatment assignment will occur on the day of the activation and after all baseline data has been collected, eligibility has been confirmed and the device has been implanted. On the day of the activation, the FCE will check the central allocation sequence and program the patient accordingly.

Until the primary endpoint is reached, subjects will be required to remain in their assigned treatment arm and not undergo reprogramming that is a departure from their assigned treatment group. If the subject reports that the stimulation in their current treatment arm is uncomfortable and requests reprogramming, a protocol deviation will be required, and the patient may not be considered in the primary analysis population.

If unblinding has occurred, the circumstances around the unblinding must be documented on an unblinding CRF and the Sponsor notified as soon as possible.

5.4. Schedule of Assessments

The enrollment process consists of obtaining informed consent, screening, completing baseline evaluation, implanting the eCoin system, and establishing the participant's amplitude setting. Follow up assessments will occur at 2- and 3-months post activation. The patient and investigator unblinding will occur at the end of the 3 months visit and a final follow up visit will occur at 4 months post-activation. A revision procedure would not reset the initial activation date.

For visits involving a 3-day voiding diary, the diary should be completed over 3 consecutive days during the 7 days prior to the indicated visit. The timing windows associated with each visit number is described below.

- Visit 1: Screening Procedures (informed consent, demographic and medical history and concomitant medication/therapy information, physical examination, and vital signs are collected, subjects begin 2 week wash-off of OAB medications or 4 week wash-off of PTNS if applicable, eligibility determination)

- Visit 2: Baseline Assessments (3-day voiding diary, OABq, patient satisfaction survey, concomitant therapy review, final eligibility determination) (Time: Between 3 and 32 days from Visit 1)

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- Visit 3: Implant Procedure (vital signs collected, adverse event assessment, concomitant therapy review, pictures taken) (Time: Between 0 and 20 days from Visit 2)

- Visit 4: Incision Healing Check (vital signs collected, adverse event assessment, pictures taken, concomitant therapy review) (Time: Between 9 and 19 days from Visit 3)

- Visit 5: Initial Activation and Randomization at Sensory or Subsensory (vitals signs collected, adverse event assessment, pictures taken, concomitant therapy review) (Field Clinical Engineer present)) (Time: Between 23 and 43 days from Visit 3)

- Visit 6 (2 months post-activation): Follow-up assessments (3-day voiding diary, OABq, patient satisfaction survey, adverse event assessments, concomitant medication therapy review) (Time: Between 7 and 9 weeks from Visit 5)

- Visit 7 (3 months post-activation): Follow-up assessments (3-day voiding diary, OABq, patient satisfaction survey, adverse event assessments, concomitant medication therapy review, unblinding and reprogramming as requested (Field Clinical Engineer present)) (Time: Between 12 and 14 weeks from Visit 5)

- Visit 8 (4 months post-activation): Follow-up assessments (3-day voiding diary, OABq, end of study survey, adverse event assessments, concomitant medication therapy review) (Time: Between 16 and 18 weeks from Visit 5)

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	Screening	Baseline	Implantation	Incision Healing Check	Activation (Follow up Clock Starts)	2 Month	3 Month: Primary Endpoint	4 Month
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
3-day Voiding Diary		X				X	X	X
OABq Assessment		X				X	X	X
Patient Satisfaction Survey		X				X	X	
End of Study Survey								X
Implant Procedure			X					
Incision Assessment				X				
Pictures Taken			X	X	X			
Vitals Taken	X		X	X	X			
Programming					X		X	
Randomization					X			
Completion of Primary Endpoint/Unblinding							X	
Completion of Study								X
Subject Assessment for AEs		X	X	X	X	X	X	X
Concomitant Medication Therapy Review	X	X	X	X	X	X	X	X

5.5. 3-day Voiding Diary

Throughout the study, subjects will complete 3-day voiding diaries to quantify voiding behavior, symptoms, and incontinence. The diary should be completed over three consecutive days during the seven days prior to each visit, involving a 3-day diary. The site should telephone subjects to remind them of the diary requirement at least

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three days prior to each visit. Training on the diary completion will be provided by the Sponsor to the site personnel. The voiding diaries will collect the following information every day over 3 days:

- total number of leaks
- total amount leaked
- total number of urge leaks

All reasonable efforts will be made to ensure that all diaries are completed over the full three-day period. Incomplete and missing diaries will be handled according to section 8.6 Missing Data.

5.6. Patient Surveys

The Overactive Bladder Symptom Quality of Life Questionnaire (OABq) will be administered at baseline, 2 months, 3 months, and 4 months after activation. The patient satisfaction survey will be administered at baseline, 2 months, and 3 months after therapy. The eCoin End of Study survey will be administered at the 4 month post-activation visit only.

5.6.1. Health Related Quality of Life portion of the Overactive Bladder Symptom Quality of Life Questionnaire (OABq)

The Health-Related Quality of Life (HRQL) portion of the Overactive Bladder questionnaire (OABq) consists of 25-item questionnaire. The full Overactive Bladder questionnaire consists of a 33-item questionnaire. The full survey will be administered at baseline and 2, 3, and 4 months post-activation, however only the HRQL portion will be analyzed. Each question is scored using a six-point scale, with higher scores indicating more severe symptoms or poorer quality of life.

5.6.2. eCoin Satisfaction Survey

The eCoin satisfaction survey consists of questions and 4 statements for assessment of agreement and rates each subject's satisfaction with their symptoms and therapy. This survey uses 7-point Likert scale responses. Some

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questions/statements have N/A options. The subject is asked to reflect on two different time points, in the current moment, and over the past month.

5.6.3. Study Exit Survey

The Study Exit Survey consists of 1 question and 4 statements for assessment of agreement carried over from the patient satisfaction survey plus an additional 4 statements for assessment of agreement applicable to the end of study. This survey uses 7-point Likert scale responses. Some questions/statements have N/A or "Not familiar" options.

6. Sample Size Determination

This study will explore the effect of two programming methodologies (sensory and subsensory amplitude) on reduction of UUI episodes per day as compared to baseline. Change of average UUI per day at 3-months follow-up will be summarized with descriptive statistics for each study arm.

As detailed below, the minimum sample size required for this study is 32 subjects (16 per arm). The planned enrollment of 40 subjects implanted and up to 50 meets this minimum. From the pivotal study, a total of n=133 patients were implanted with eCoin. Looking at the subset of patients programmed at or below sensory level, after 8 weeks of therapy there was a mean reduction in UUI episodes of 2.3 with a standard deviation of 1.4, After 12 weeks of therapy, there was a mean reduction in UUI episodes of 2.7 with a standard deviation of 1.8 per day (n=22). Based on a confidence interval using a t-distribution, a two-sided type-I error rate of 0.05, and using a standard deviation of 2, precision was calculated for a range of sample sizes using the equation below based on the PASS One Mean Module with Tolerance Probability. Margin of error, also known as precision, is the distance between the mean and edge of an interval.

$$D = \frac{t_{1-\propto/2,n-1} * \hat{\sigma}}{\sqrt{n}}$$

Sample Size	Precision
13	1.21
14	1.15
15	1.11

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16	1.07
17	1.03
18	0.99
19	0.96
20	0.94

*Standard deviation=2

We plan to use the per protocol population as our primary analysis population. This is due to the concern that the Intent to Treat (ITT) population will be diluted due to deviations from the assigned therapy. To adjust for noncompliance/nonadherence, we must estimate the proportion from the subsensory group who will have a sensory level that is cannot be reduced by 25% (i.e. their sensory threshold is the minimum setting of 0.5 mA). Based on the Pivotal trial, 3.85% (n=130) had a sensory threshold of 0.5 mA. Since this scenario only affects the subsensory arm, we estimate this this proportion to be 0.02. Additionally, in the subsensory threshold group, we must adjust for patients who have no sensory threshold, (i.e. they do not feel sensation at any amplitude level and therefore are unable to identify the sensory setting). Based on the Pivotal trial, 6.15 % (n=130) had a sensory threshold of “not identified.” Since this scenario only affects the sensory arm, we estimate this scenario to be 0.03. Lastly, we plan for a 10% dropout rate.

Considering the scenarios described above, a sample size of n=16 will have a precision of 1.07. For this analysis, we are considering a low assumed treatment effect as a mean reduction of 1.3. This is the 3rd quartile of mean reduction from the pivotal trial at 2 months, meaning 75% of the data lies below -1.3. The mean reduction from 8 weeks is being used for this analysis because in the pivotal study, patients had the option to reprogram at 8 weeks, therefore the 12 week results are confounded by reprogramming. Since the precision of 1.07 is below our assumed treatment effect of 1.3, the confidence interval (0.23, 2.37) does not include zero. This means if the treatment is effective, we expect to have sufficient sample size to see a result. Accounting for 15% of patients taken out of the Per Protocol population due to withdrawal or deviations from the assigned therapy group, a sample size of 13 per arm has a precision of 1.21 which is less than 1.3 UUI.

7. Analysis Populations

Efficacy analyses will be generated for the ITT and Per Protocol (PP) Population. Safety data will be reported on all enrolled subjects who undergo a procedure from implantation of the study device. Figure 1, below shows the patient disposition schema for each of the analysis populations.

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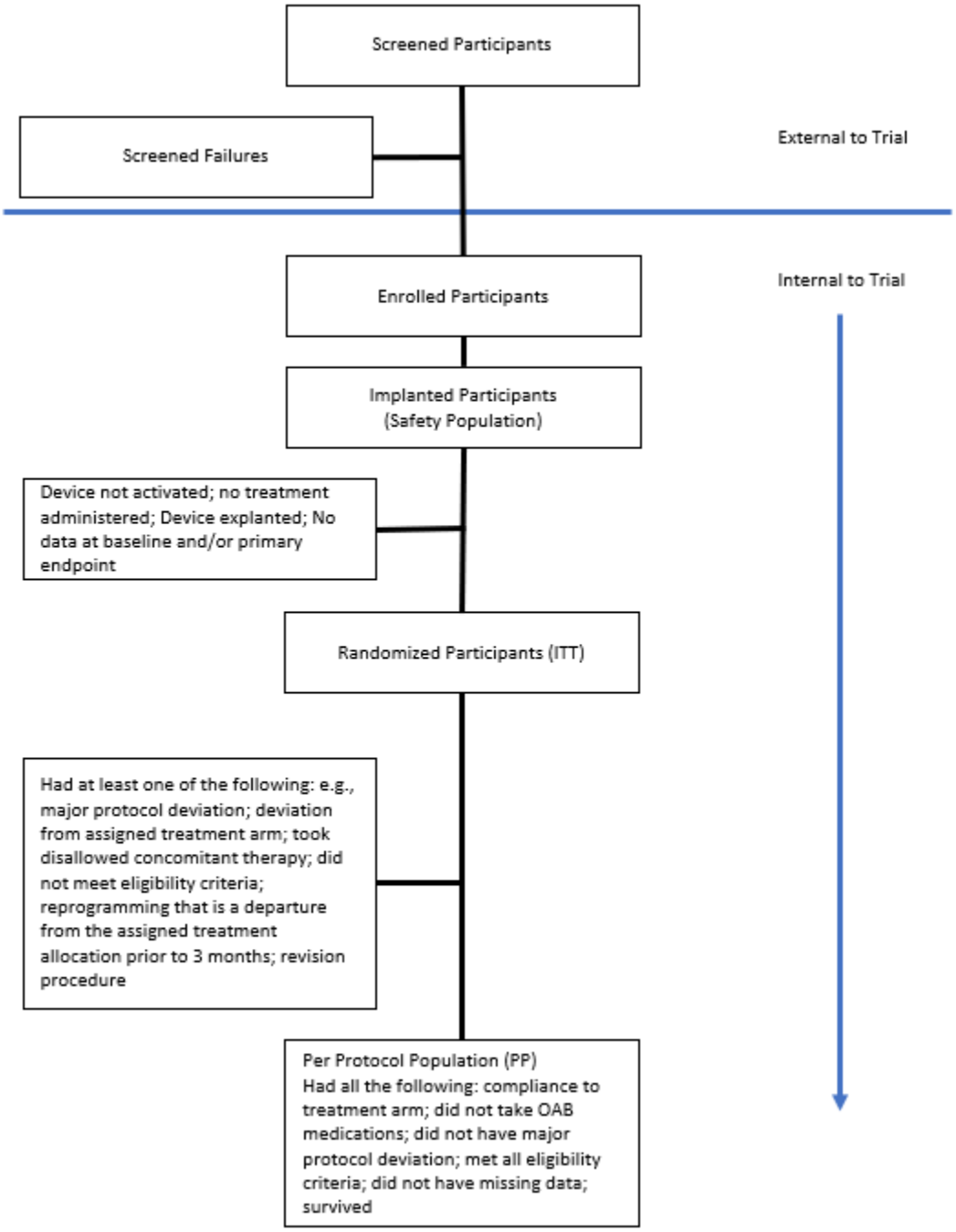
Figure 1 Analysis Populations



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7.1. Per Protocol Population

The Per Protocol population will include all subjects in the Intent to Treat population with no major protocol deviations. Subjects in the PP population must remain OAB drug-free for the duration of the study. Additionally, subjects should not have any significant departures from the amplitude programming. This is the primary and secondary endpoint analysis population.

7.2. Intent-to-Treat

All enrolled subjects who undergo a procedure for implantation of eCoin and are randomized to a treatment arm and who have data available at the baseline and primary endpoint.

7.3. Safety Population

All enrolled subjects that undergo a procedure for implantation of eCoin. This will be the primary analysis population for the safety analysis.

8. General Statistical Conventions and Considerations

Descriptive statistics will summarize results of the ESSENCE protocol. Standard descriptive statistics, such as number of subjects, mean, standard deviation, quartiles, minimum, and maximum, will be calculated for continuous variables. For discrete variables, summary tables will display numbers of subjects and related percentages. Tables will display three columns of results showing all data as well as the sensory and subsensory treatment arms. The general statistical conventions and definitions used for the data analysis are described below.

8.1. Key Definitions

8.1.1. Baseline

Baseline efficacy measures will be defined as the last measure taken up to and including the baseline visit (Visit 2). Baseline safety measures will be defined as the last measure taken prior to device implantation.

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8.1.2. Diary Data

8.1.2.1. UUI Episodes

A UUI episode is defined as a leak that is not being caused by physical movement as indicated on the voiding diary.

8.1.2.2. Total Leakage

Total leakage is defined as any leak (stress or urge) as indicated on the voiding diary.

8.1.2.3. Amount of Accidental Urine Leakage

Amount of accidental urine leakage is defined as the total leakage volume categorized as small, medium, and large leaks and calculated in the Database using the calculation:

1 X Small leak + 2 X Medium Leak + 3 X Large Leaks.

8.1.3. Diary Completion

A voiding diary is considered complete if the CRF question “Did the subject adequately complete the 72-hour diary” is answered “yes.” Diaries may be redone, reconciled, and averaged as described in section 8.6.3 Missing or Incomplete Diary.

8.1.4. Study Exit

A subject’s study exit date will be defined as the study exit date on the study exit CRF.

8.1.5. Study Completion

A subject will be defined as “completed” if he/she completes the 4-month post-activation study visit.

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8.2. Derived variables

8.2.1. Age

Age in years will be calculated as the integer portion of the following:

[(Date of enrollment- Date of birth) + 1] / 365.25

8.2.2. BMI

BMI will be calculated using the following equation:

703 X [(Weight in pounds)/(Height in inches^2)]

8.2.3. Study Days

For the analysis, study day will be calculated relative to device implantation or initial activation, depending on the analysis:

- Study day relative to implantation = date of visit/test – implantation date + 1.
- Study day relative to activation = date of visit/test – activation date + 1.

If the date of a visit or test occurs before the date of interest, then study day = date of visit (or test) – implantation/activation date. The study does not define a Day 0.

8.2.4. UUI Episodes per Day

UUI episodes per day will be calculated as an average over 3 days.

UUI episodes per day = (UUI Day 1 +UUI Day 2+ UUI Day 3)/3

8.2.5. Change from Baseline

Change from baseline will be calculated for the key primary and secondary endpoints for both UUI data and HRQL data.

Change from baseline will be calculated as follows:

CFB= Post-baseline UUI Episodes per day– UUI Episodes per day at baseline

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For HRQL data, change from baseline will be calculated using the composite score as follows:

CFB: Post-baseline composite score- Baseline composite score

8.3. Timing of Analysis

8.3.1. Interim Analysis

No interim analysis is planned for this study.

8.3.2. Primary Endpoint Analysis

The primary analysis will be performed after all subjects complete 3 months of therapy. The analysis will be performed on a locked Excel database that has been documented as meeting the cleaning and approval requirements of the DMP. Analysis will occur only after this SAP has been approved and a database lock form has been completed. The primary analysis may include but is not limited to:

- Study population summaries
- Primary efficacy outcome
- Secondary efficacy outcome through 3 months post-activation

8.3.3. End of Study Analysis

A final analysis will be performed after all subjects complete 4 months of therapy and are exited from the study. The analysis will be performed on a locked Excel database that has been documented as meeting the cleaning and approval requirements of the DMP. Analysis will occur only after this SAP has been approved and the second database lock has been documented. The secondary analysis may include but is not limited to:

- Study population summaries
- Secondary efficacy outcome after 4 months of therapy
- Sensitivity and additional analysis
- Exploratory subgroup analysis

8.4. Changes to Planned Analysis

Changes to the analyses described in this plan will be fully documented in a revised version of the plan written prior to locking the study database and conducting the primary outcome analysis. Changes should be documented and approved before

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unblinding occurs. Changes made after locking the study database will be described in the clinical study report and characterized as “exploratory”.

8.5. Center Pooling

The ESSENCE study is a multi-center study and data from all study centers will be pooled for analysis. There are no planned statistical methods to test for treatment-by-center interactions.

8.6. Missing Data

8.6.1. Premature discontinuation from the study

Any subject that does not have follow-up data at the timepoint being analyzed will be excluded from the dataset.

8.6.2. Incomplete Dates

Completely missing dates will not be imputed.
Partial dates in the medication and adverse events data will be imputed. Partial start dates will be imputed as follows:

- Dates with only missing day will be imputed to the first of the month; however, if the month and year of the partial date are the same as the month and year of the device implantation date, the partial start date will be imputed to the device implantation date.
- Dates with missing day and month will be imputed to January 1st of the given year; however, if the year of the partial date is the same as the year of the device implantation date, the partial start date will be imputed to the device implantation date.

Partial end dates will be imputed as follows:

- Dates with only missing day will be imputed to the end of the month.
- Dates with missing day and month will be imputed to December 31st of the given year.

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8.6.3. Missing or Incomplete Diary

All reasonable efforts will be made to ensure that all diaries are completed over the full three-day period. Any incomplete diaries with data available for 2 out of 3 days will be reported and averaged over the total days in which they were completed.

In some cases, patients may be required to redo their diary. Examples of these scenarios are described below:

- It is missing more than 1 day of data entry
- It is filled out incorrectly and unable to be reconciled
- It is illegible and unable to be reconciled
- It is considered incomplete at the discretion of the site staff

In these scenarios, the revised diary data and associated dates will prevail over the original and will be included in the analysis.

If a subject is unwilling or unable to complete or reconcile and incomplete diary, their data will be excluded from the analysis.

A CRF field will exist on the baseline and follow-up CRFs asking whether the diary is complete. If a diary is redone or reconciled, this box should be changed from “no” to “yes.” If the diary is missing or irreconcilable, this box should be checked “no.” Reconciliation efforts and/or diary redo scenarios should be documented in protocol deviation forms.

8.6.4. Missing or Incomplete Survey Data

No data imputations will be performed for missing or incomplete survey data.

9. Study Population Summaries

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

9.1. Subject Disposition

Tables will present the number and percentage of subjects who fall into each of the following categories. Tables will include all subjects and the sensory and subsensory treatment arm where applicable.

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- Total enrolled (all subjects)
- Total implanted (safety population-all subjects)
- Total enrolled subjects who undergo a procedure for implantation of eCoin and are randomized to a treatment arm and have data at baseline and the primary endpoint. (ITT population-all subjects, sensory arm, subsensory arm)
- Total subjects that undergo a procedure for implantation of eCoin and are randomized to a treatment arm, experience no major protocol violations or deviations from assigned therapy (Per protocol population-all subjects, sensory arm, subsensory arm)
- Early termination from the study (all subjects)
- Completed study (all subjects)

For subjects who withdraw from the study early, the number and percentage withdrawing by reason will be presented. A by-subject listing of early terminations will be presented including the last study visit completed and reason for early termination. A subject disposition flow and study schedule time points will summarize all enrolled subjects who reached various stages of the trial and their analysis population.

9.2. Subject Eligibility

Inclusion and exclusion criteria not met at screening (screen failures) will be presented for all screened but not enrolled subjects. Eligibility not met for enrolled subjects will also be presented. Eligibility data will be summarized in a table with the number (n) and percentage of subjects that did not meet each criterion. Subjects can be counted under multiple rows.

9.3. Randomization

Randomization details will be listed for all subjects in the ITT population. This listing will include the date of randomization, randomization number, block, and assigned treatment arm.

9.4. Premature Unblinding

The ESSENCE protocol requires patient and investigator blinding through 3 months post-activation. A by subject listing of all premature unblinding will be presented. This table will include the date of the unblinding, who was unblinded (patient vs Investigator), and the circumstances surrounding the event.

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9.5. Protocol Deviations

Protocol deviations, which are collected throughout the study, will be summarized. A major protocol deviation is one that affects the safety of the subject or the scientific validity of the results. A minor deviation does not affect the safety of the subject or the scientific validity of the results. The frequency and percentage of patients with at least one major Protocol Deviation and minor Protocol deviation will be listed by classification and reason/category for the PD.

9.6. Treatment Compliance

The ESSENCE study will explore the effect of sensory and subsensory treatment arms. Significant departures from the assigned amplitude programming protocol include:

- no sensory level identified for the sensory arm
- sensory level identified at the lowest amplitude setting (0.5 mA) for the subsensory arm
- reprogramming visit prior to 3 months that is a significant departure from the assigned treatment stimulation
- device not activated
- device turned off
- A protocol deviation related to device programming does not match assigned treatment arm

Any non-compliances to the assigned treatment arm at randomization will be listed by subject. This listing will include the date of randomization, assigned treatment arm, and reason for departure, and date of treatment noncompliance.

9.7. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by age, gender, ethnicity, race, current smoking status. Demographic and baseline characteristics will be summarized for all implanted subjects. Percentages will be calculated relative to the number of subjects in the population being presented.

OAB history will be presented. History will include duration of OAB and success of prior treatments (PTNS therapy, TENS therapy, OAB medications, and Botox. It will include duration of OAB and success of prior treatments (PTNS therapy, TENS therapy, OAB medications, anti-stress incontinence surgery, and Botox). Success will be categorized as “yes”, “no”.

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Additionally, a by-question listing of multiple-choice questions on the CRF pertaining to the subject's experience with OAB will be summarized for all implanted subjects.

9.8. Treatment Exposure

The duration of device implantation and device activation, in weeks, will be summarized for all implanted subjects.

10. Efficacy Analysis

10.1. Primary Efficacy Analysis:

This randomized controlled double-blind study will evaluate the efficacy of eCoin in reducing episodes of UUI per day with two different treatment arms. The primary efficacy outcome is the reduction from baseline in the number of UUI episodes per day on a 3-day voiding diary (72 hours) after 3 months of eCoin device tibial nerve stimulation. The voiding diary CRF will report the total over the 3 days for each measure, which will then be averaged.

The primary efficacy analysis will be performed on the Per Protocol population. The change from baseline will be summarized with descriptive statistics (n, mean, median, standard deviation, 25th quartile, 75th quartile, minimum, and maximum). Additionally, the mean reduction of UUI episodes per day along with its two-sided 95% confidence interval will be summarized for all subjects, sensory arm, and subsensory arm. Boxplots and line graphs with observed values and change from baseline may also be presented. Treatment effect size may be reported using Cohen's d and/or relative risk to highlight the observed differences, if any.

No data imputations will be performed for subjects who do not have 3-month post-activation data. Missing and incomplete diary data will be handled per section 8.6.3 Missing or Incomplete Diary.

The primary endpoint is exploratory in nature. There are no pass/fail criteria to define the study success and there is no powered comparison between the two treatment arms

Because this study is exploring the efficacy of the eCoin System programmed using two different methodologies, the per protocol population will be analyzed for the primary endpoint. The per protocol population, as described in section 7. Analysis Populations, will exclude patients that have taken OAB medications, do not meet eligibility criteria, experience major protocol deviations and/or experience departures

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from the assigned programming treatment. Due to the nature of the study, it is expected a subset of all implanted subjects will have data on the primary endpoint.

10.2. Secondary Efficacy Analysis

The primary efficacy analysis will be performed on the Per Protocol population. The change from baseline in Health-related Quality of Life (HRQL) score will be summarized with descriptive statistics. The HRQL is a subset scale of 25 questions. The numbers presented represent transformed composite scores, ranging from 0-100. Boxplots with observed values and changes from baseline may also be presented. Data will be summarized at 2, 3, and 4 months of therapy a by all subjects and in each treatment arm in the per protocol population. Missing data will not be imputed for subjects that do not have HRQL scores at each given timepoint.

The reduction from baseline in number of UUI episodes per day on a 3-day diary will be summarized with descriptive statistics (n, mean, median, standard deviation, 25th quartile, 75th quartile, minimum, and maximum after 2, and 4 months of eCoin tibial nerve stimulation. The voiding diary CRF will report the total over the 3 days for each measure, which will then be averaged. Boxplots with observed values and change from baseline may also be presented for all subjects and each treatment arm in the per protocol population. Data will be summarized at 2 and 4 months of therapy. Missing data will be handled the same as for the primary endpoint.

Observed answers for the patient satisfaction survey will be pooled by question. Data will be summarized at baseline, 2, 3, and 4 months of therapy and by all subjects and each treatment arm in the per protocol population. Missing data will not be imputed for these analyses.

10.3. Sensitivity and Additional Analysis

The primary and secondary efficacy analysis will be repeated the ITT population. There is no planned sensitivity analysis for missing data.

10.4. Exploratory Subgroup Analysis

10.4.1. Responders

The proportion of subjects who respond to treatment (achieve at least a 50% reduction from baseline in the number of UUI episodes per 24 hours on a 3-day voiding diary after 3 months of eCoin tibial nerve stimulation) will be summarized for all subjects, the sensory arm, and subsensory arm from the per protocol population.

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10.4.2. Blinded subgroup

The blinded population will include all the subjects in the ITT population that maintain the investigator and patient treatment blind through 3 months post-activation. Subject unblinding will be tracked through the completion of the Unblinding Case Report Form (CRF). The primary and secondary efficacy endpoints will be repeated on the blinded population.

11. Safety Analysis

11.1. Related AEs and SAEs

Adverse events (AEs) and Serious Adverse events (SAEs) will be continuously monitored throughout the study. Investigators will classify each AE according to its relationship to study device. All device- and procedure-related adverse events and all SAEs up to 4 months after activation will be summarized. AEs will be coded using version 25 or later of the MedDRA dictionary and summarized by System Organ Class and Preferred Term. Tabulations of device- and procedure-related AEs and SAEs which will be provided by time point, will include the number of (S)AEs, the number of subjects who experienced the S(AE), and the percent of subjects who experienced the S(AE

The safety population will be used for all AE analyses. The following presentations of treatment-emergent adverse events will be generated:

- All AEs related to study procedure up 4 months post-activation
- All AEs related to study device up to 4 months post-activation
- All SAEs up to 4 months post activation

12. Quality Assurance of Statistical Programming

Statistical programming code that affects the results of the key primary and secondary endpoints will be validated and documented prior to conducting the analysis. The programming code will be validated in two stages. A peer reviewer external to the study team will review and statistical program and provide feedback. Findings will be documented through meeting minutes. The second stage will be to cross-verify results using test data. This includes independently reproducing selected analysis results to validate the accuracy of the statistical program's output.

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Results obtained from the program will be compared with those generated from a by hand calculations.

References

1. Amundsen CL, Richter HE, Menefee SA, et al. (2016). OnabotulinumtoxinA vs sacral neuromodulation on refractory urgency urinary incontinence in women: a randomized clinical trial. *JAMA* 316(13):1366–1374.

2. Siegel S, Noblett K, Mangel J, et al. (2015). Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. *Neurourology and Urodynamics* 34 (3): 224-230.13

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