Official Title of the study: Vectors Post Market: A study to assess pain relief using spinal cord stimulation with high dose stimulation parameters

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Statistical Analysis Plan

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Table of Contents

1.   Version History

Version	Summary of Changes	Author(s)/Title
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2.   List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AGA	Activity Goal Assessment
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigation Plan
CONSORT	Consolidated Standards of Reporting Trials
DD	Device Deficiency
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol Five Dimensions Questionnaire
HD	High Dose
MedDRA	Medical Dictionary for Regulatory Affairs
MI	Multiple imputations
MUO	Medtronic Use Only
NANS	North American Neuromodulation Society
NPU	Neuro Programmer Upload
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
PM	Post-Market
PT	Preferred Term (classification within MedDRA)
SAP	Statistical Analysis Plan
SCS	Spinal Cord Stimulation
SOC	System Organ Class (classification within MedDRA)
SSA	Subject Satisfaction Assessment
UK	United Kingdom
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale

3. Introduction

The Vectors Post Market (PM) study is a global, prospective, single-arm, multi-center, open label study evaluating the efficacy of spinal cord stimulation (SCS) therapy for pain relief using high dose (HD) stimulation parameters while targeting a specific anatomical location.

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the planned analyses of the objectives listed in the study Clinical Investigation Plan (CIP). This SAP is comprehensive of the statistical methods and analyses to be included in the final study report. Unless otherwise specified, all analyses listed within this SAP will be included in the final study report. ███████████
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4. Study Objectives

4.1. Primary Objective

To demonstrate a significant improvement in overall (low back and leg) pain intensity using HD stimulation starting at 90 - 200 µsec and 1000 Hz with lead placement spanning the T9/T10 disc space, as measured by the Visual Analog Scale (VAS), from Baseline to the 3-Month Visit.

4.2. Safety Assessment

This study will characterize all device-, therapy-, or procedure-related adverse events and device deficiencies from enrollment to study exit.

4.3. Secondary Objectives

1. To characterize the overall (low back and leg) pain efficacy responder rate, as measured by the VAS, from Baseline to the 3-Month Visit, with a confidence interval within ± 10%
2. To characterize the low back pain efficacy responder rate, as measured by the VAS, from Baseline to the 3-Month Visit, with a confidence interval within ± 10%
3. To characterize the leg pain efficacy responder rate, as measured by the VAS, from Baseline to the 3-Month Visit, with a confidence interval within ± 10%

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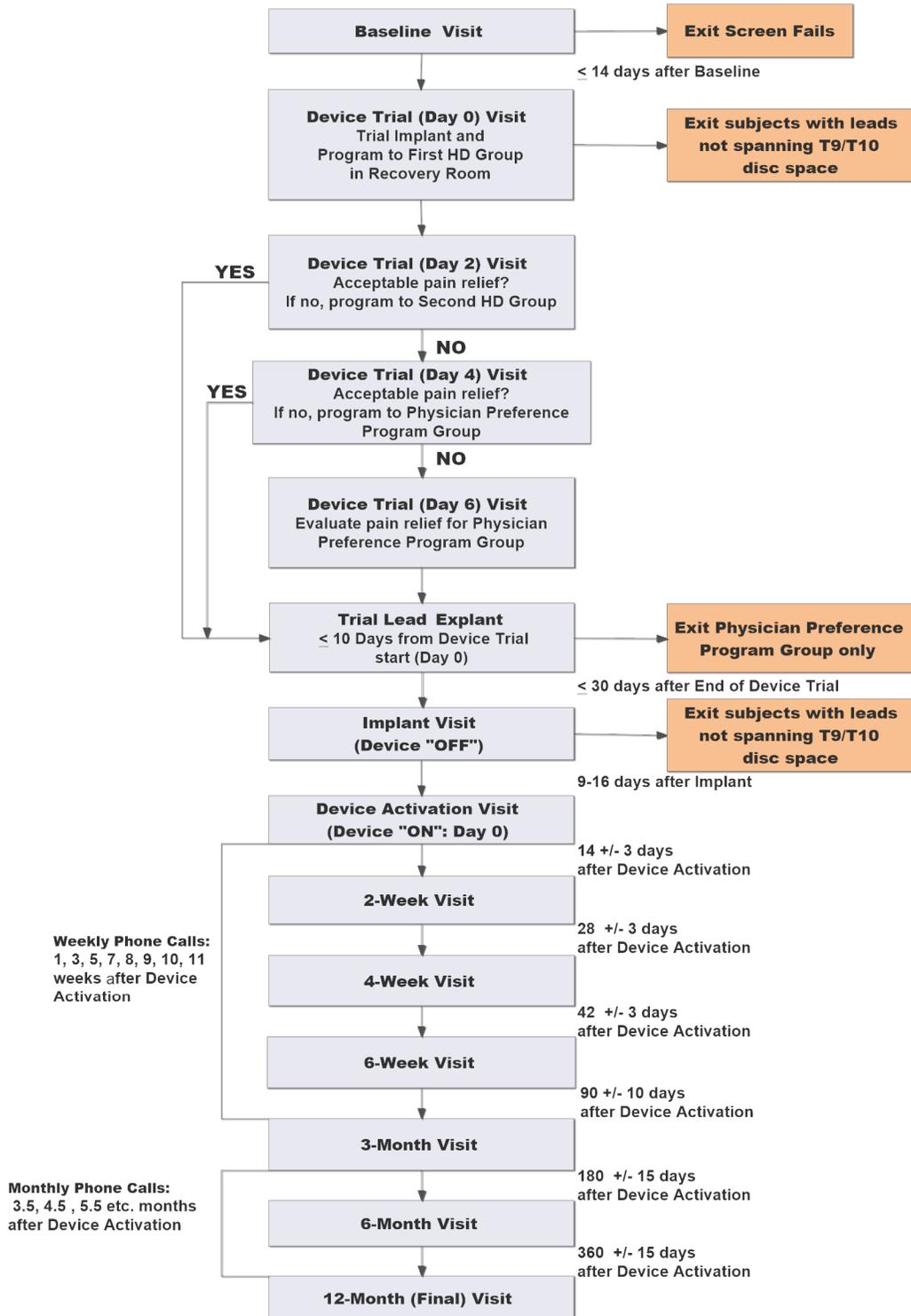
5.   Investigation Plan

This is a global, prospective, single-arm, multi-center, open label study evaluating the efficacy of SCS therapy for pain relief using HD stimulation parameters while targeting a specific anatomical location. The study will be conducted at up to 30 centers globally.

To be enrolled in the study, adult patients must have both low back and leg pain of at least 50mm (out of 100mm) on the Visual Analog Scale (VAS), and an Oswestry Disability Index (ODI) score from 21 to 80 (out of 100). They must be on stable pain medications for the treatment of their pain and be willing to not increase these medications through the 3-Month Visit.

Subjects who meet the inclusion and exclusion criteria at Baseline undergo a trial lead implant procedure. At Device Trial, if the final lead placement after paresthesia mapping spans the T9/T10 disc space, the subjects may continue in the study. Subjects using HD stimulation settings with a self-reported pain improvement of at least 50% at Day 2 or Day 4 of the trial are then eligible to receive a permanent SCS implant within the study.

Once implanted with a permanent SCS system, if the final lead placement spans the T9/T10 disc space, the subject continues in the study with the following visits: Device Activation, 2-Week, 4-Week, 6-Week, 3-Month (Primary and Secondary objectives visit), 6-Month, and 12-Month, with a planned phone call between each visit. Subjects will discontinue from the study following the 12-Month Visit. Figure 1 shows the study visits from Baseline through the 12-Month Visit.

Figure 1. Vectors PM study visit flowchart

Figure 1. Vectors PM study visit flowchart

Baseline Visit → Exit Screen Fails

≤ 14 days after Baseline

Device Trial (Day 0) Visit
Trial Implant and
Program to First HD Group
in Recovery Room → Exit subjects with leads not spanning T9/T10 disc space

Device Trial (Day 2) Visit
Acceptable pain relief?
If no, program to Second HD Group — YES / NO

Device Trial (Day 4) Visit
Acceptable pain relief?
If no, program to Physician Preference Program Group — YES / NO

Device Trial (Day 6) Visit
Evaluate pain relief for Physician Preference Program Group

Trial Lead Explant
≤ 10 Days from Device Trial start (Day 0) → Exit Physician Preference Program Group only

≤ 30 days after End of Device Trial

Implant Visit (Device "OFF") → Exit subjects with leads not spanning T9/T10 disc space

9-16 days after Implant

Device Activation Visit (Device "ON": Day 0)

14 +/- 3 days after Device Activation

2-Week Visit

28 +/- 3 days after Device Activation

4-Week Visit

42 +/- 3 days after Device Activation

6-Week Visit

90 +/- 10 days after Device Activation

3-Month Visit

180 +/- 15 days after Device Activation

6-Month Visit

360 +/- 15 days after Device Activation

12-Month (Final) Visit

Weekly Phone Calls: 1, 3, 5, 7, 8, 9, 10, 11 weeks after Device Activation

Monthly Phone Calls: 3.5, 4.5 , 5.5 etc. months after Device Activation

6. Determination of Sample Size

The sample size for this study has been determined by the secondary objectives, which are to characterize a responder rate with a confidence interval within ± 10%. Calculations were performed using PASS11, Confidence Intervals for One Proportion, with Confidence Level = 0.95, P = 0.5, Confidence Interval Formula = Score (Wilson), Interval Type = Two-Sided. Table 1 shows the 95% confidence interval for a 50% responder rate for 50-100 subjects. A sample size of 100 subjects provides a 95% confidence interval within 9.6% of the responder rate estimate, if the observed responder rate is 50%. The confidence interval is the widest with a responder rate of 50%; a lower or higher responder rate will have a narrower confidence interval.

Table 1. 95% Confidence Interval (CI) for Responder Rate = 50%

N	Lower Limit	Upper Limit	CI Width	+/- Range
50	36.6%	63.4%	26.7%	13.4%
60	37.7%	62.3%	24.5%	12.3%
70	38.6%	61.4%	22.8%	11.4%
80	39.3%	60.7%	21.4%	10.7%
90	39.9%	60.1%	20.2%	10.1%
100	40.4%	59.6%	19.2%	9.6%

Calculations using PASS11 show a required sample size of 26 subjects for the primary objective: Tests for One Mean, alpha = 0.05, power = 0.9, null mean (Mean0) = 0, alternative mean (Mean1) = 20, standard deviation = 30, alternative hypothesis = Mean0 ≠ Mean1, and Infinite population size. A sample size of 100 subjects derived for the secondary objectives ensures over 99% power under these same assumptions.

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7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition will be summarized by site and overall in a table showing the number of subjects at these visits: Baseline, Trial Day 0, Implant, Activation, 3-Month, 6-Month, and 12-Month. Additionally, the subject disposition at each visit will be depicted in a flow diagram. For subjects within the Trialed Analysis Set (see section 7.1.3), the number who report at least a 50% improvement in pain at the Trial Day 2, Day 4, and Day 6 Visit will be summarized.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be summarized by deviation type and associated visit. A listing of protocol deviations, which will include the reason for the deviation and any other additional details about the deviation, will also be included in the final study report.

7.1.3.   Analysis Sets

There will be 4 population sets for the purposes of analysis in this study.

Enrolled Analysis Set: All consented subjects.

Trialed Analysis Set: All subjects who have a Device Trial Day 0 Visit.

Implanted Analysis Set: All subjects who have a positive device trial with HD parameters at T9/T10 and are implanted with a neurostimulation system.

Treated Analysis Set: All subjects in the Implanted Analysis Set whose devices are activated at the Device Activation Visit.

7.2. General Methodology

Summary statistics will be presented for continuous measures (N, means, medians, standard deviations, minimums and maximums) and categorical measures (N, percent, frequency distributions) with two-sided 95% confidence intervals as appropriate. Tests of change from baseline will use the one-sample paired t-test. The score (Wilson) method will be used to calculate the 95% confidence intervals of responder rates and percentages of subjects.

All analyses will be pooled by neurostimulator model unless otherwise specified.

7.3. Center Pooling

Data will be pooled across centers for all analyses. No single site may implant more than 25 subjects. This is intended to reduce the possibility that a site with atypical results will be overly influential in the study results based on pooled data.

Summary statistics of the primary, secondary, and safety assessments will be reviewed by center. This analysis will not be included in the final clinical study report unless there is high variability in results across centers.

7.4. Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be included in the data listings and tabulations.

Imputation of values for missing pain scores for primary and secondary efficacy analyses will be performed as follows. For scheduled follow-up visits with missing VAS pain scores, if an Unscheduled Visit occurred within the scheduled visit window, and the VAS pain scores were collected at that Unscheduled Visit, the VAS pain scores from the Unscheduled Visit will be used in the analyses of that scheduled visit. Otherwise, the missing VAS pain scores will be imputed using multiple imputations (MI).
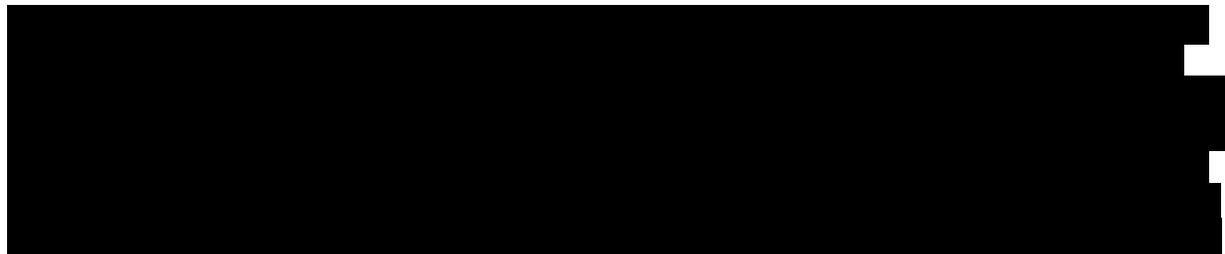
Following imputation, the objectives will be evaluated using MI analysis methods.

7.5. Adjustments for Multiple Comparisons

The study has one primary objective that will be evaluated with statistical testing. The primary objective will be evaluated with statistical testing at the alpha=0.05 level after all subjects in the Treated Analysis Set have completed the 3-Month Visit. The secondary objectives are not alpha-controlled; they will be characterized but not evaluated with statistical testing.

7.6. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the Enrolled, Trialed, and/or Treated Analysis Sets (section 7.1.3) as appropriate. Subjects with missing or unknown demographic data will be excluded from the relevant analysis, with a count of subjects with missing data provided. Listings of all demographic and baseline characteristics will be included.

7.6.1. Demographics

Age at consent, in years, will be calculated as the difference between the first consent date and the subject's date of birth, using the following formula: (CONSENTDATE – BIRTHDATE)/365.25.

Age will be summarized using descriptive statistics such as mean, standard deviation, minimum, and maximum.

Categorical demographics (sex, ethnicity, and race) will be summarized as counts and percentages. If more than one race is selected for a subject, this be counted as "Multiple" in the race summary, and additional details will be provided separately for these subjects.

7.6.2. Baseline Characteristics

Years from onset of chronic intractable pain to enrollment will be calculated as:

Year of first consent date – Year of onset for chronic intractable pain of the low back and leg

Years from pain onset will be summarized using descriptive statistics such as mean, standard deviation, minimum, and maximum.

Primary diagnosis will be summarized as a count and percentage.

The number of prior surgical procedures will be counted per subject, with each row in Surgical History being counted as one procedure. For subjects where it is indicated there is no history of surgical procedures, the number of procedures will be 0. Number of prior procedures will be summarized using descriptive statistics such as mean, standard deviation, minimum, and maximum. Additionally, a frequency distribution will be provided summarizing the number of subjects with 0, 1, 2, etc. prior surgical procedures.

The number of pain medications with a start date on or before the date of the subject's baseline pain assessment, where the medication is ongoing or has an end date after the date of baseline pain assessment will be counted per subject. For subjects where it is indicated there are no medications with a start date on or before the date of baseline pain assessment, the number of medications will be 0. Number of pain medications will be summarized using descriptive statistics such as mean, standard

deviation, minimum, and maximum. Additionally, a frequency distribution will be provided summarizing the number of subjects with 0, 1, 2, etc. medications at enrollment.

7.6.3.   Baseline Assessments

Assessments collected at baseline will be summarized as follows.

The visual analog scale (VAS) for overall pain (low back and leg), low back pain, and leg pain, will be summarized using descriptive statistics such as mean, standard deviation, minimum, and maximum. The distribution in 10-point increments from 50 to 100 will also be shown for each VAS measurement.

7.7. Treatment Characteristics

Device exposure will be quantified and summarized separately for the Trialed, Implanted, and Treated Analysis Sets. Amount of exposure will be summarized using descriptive statistics such as mean, standard deviation, sum, minimum, and maximum.

For all subjects in the Trialed Analysis Set, the number of days of device exposure will be calculated as:

Date of trialing leads explant – Date of Trialing Day 0

If the date of trialing leads explant is unavailable, and the subject discontinues from the study during the trial, study exit date will be used in place of the trialing leads explant date.

For all subjects in the Implanted Analysis Set, the number of days of device exposure between implant and device activation will be calculated as:

Date of Device Activation Visit – Date of Implant Visit

If a subject discontinues from the study after implant prior to the Device Activation Visit, the study exit date will be used in place of the Device Activation Visit date.

Months of device exposure for subjects in the Treated Analysis Set will be calculated as:

[(Cut-Off Date – Date of Device Activation Visit)/365.25]*12

Where Cut-off Date for each subject is, in order of priority:

(1) the date of permanent system explant, if applicable, or

(2) the date of study exit, or

(3) the most recent follow-up visit (scheduled or unscheduled).

Programming data from the Neuro Programmer Upload (NPU) database will be evaluated for subjects in the Treated Analysis Set to determine whether subjects ever received physician preference stimulation settings (ie, non-HD settings) during the study. For subjects who received physician preference stimulation settings, the months from Device Activation to first use of physician preference stimulation settings will be quantified.

7.8. Interim Analyses

No interim analyses are planned in this study to assess the primary objective endpoint. Interim analyses providing preliminary characterization of the secondary objectives and some additional measures may be performed prior to the analysis of the primary objective. No statistical adjustments will be made for these interim analyses, as formal hypothesis testing will not be conducted. ███████ ████████ ██

7.9. Evaluation of Objectives

7.9.1.   Primary Objective

The primary objective is to demonstrate a significant improvement in overall (low back and leg) pain intensity, as measured by the Visual Analog Scale (VAS), from Baseline to the 3-Month Visit.

7.9.1.1.   Hypothesis

The mean change in overall pain in implanted subjects (μ_c) from baseline to 3 months will be statistically significantly different from no change on the VAS scale 0-100 mm:

H$_0$: $\mu_c = 0$

H$_A$: $\mu_c \neq 0$

7.9.1.2.   Endpoint Definition

The change in overall pain will be calculated for all subjects in the Treated Analysis Set as:

Baseline overall pain – 3-Month overall pain

The baseline and 3-month overall pain scores will be collected on the VAS at the Baseline and 3-Month Visits, respectively.

7.9.1.3.   Analysis Methods

The two-sided, one sample t-test will be used to test the hypothesis of the primary objective with an alpha level = 0.05. The main analysis will include all subjects in the Treated Analysis Set. In addition to the hypothesis test, the two-sided 95% confidence interval for the average change in overall pain will be calculated and reported.

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7.9.2.   Secondary Objectives

7.9.2.1.   Secondary Objective 1: Overall pain responder rate

This secondary objective is to characterize the overall (low back and leg) pain efficacy responder rate, as measured by the VAS, from Baseline to the 3-Month Visit, with a confidence interval within ± 10%.

Endpoint definition

The responder rate will be calculated as the proportion of subjects in the Treated Analysis Set who demonstrate at least a 50% improvement in overall pain from baseline to 3 months. For each subject, percentage improvement will be calculated as:

$$\frac{(\text{Baseline overall pain} - \text{3-Month overall pain}) \times 100}{\text{Baseline overall pain}}$$

The baseline and 3-month overall pain scores will be collected on the VAS at the Baseline and 3-Month Visits, respectively. Subjects who report at least a 50% improvement in overall pain will be considered responders.

7.9.2.2.   Secondary Objective 2: Low back pain responder rate

This secondary objective is to characterize the low back pain efficacy responder rate, as measured by the VAS, from Baseline to the 3-Month Visit, with a confidence interval within ± 10%.

Endpoint definition

The responder rate will be calculated as the proportion of subjects in the Treated Analysis Set who demonstrate at least a 50% improvement in low back pain from baseline to 3 months. For each subject, percentage improvement will be calculated as:

$$\frac{(\text{Baseline low back pain} - \text{3-Month low back pain}) \times 100}{\text{Baseline low back pain}}$$

The baseline and 3-month low back pain scores will be collected on the VAS at the Baseline and 3-Month Visits, respectively. Subjects who report at least a 50% improvement in low back pain will be considered responders.

7.9.2.3.   Secondary Objective 3: Leg pain responder rate

This secondary objective is to characterize the leg pain efficacy responder rate, as measured by the VAS, from Baseline to the 3-Month Visit, with a confidence interval within ± 10%.

Endpoint definition

The responder rate will be calculated as the proportion of subjects in the Treated Analysis Set who demonstrate at least a 50% improvement in leg pain from baseline to 3 months. For each subject, percentage improvement will be calculated as:

$$\frac{(\text{Baseline leg pain} - \text{3-Month leg pain}) \times 100}{\text{Baseline leg pain}}$$

The baseline and 3-month leg pain scores will be collected on the VAS at the Baseline and 3-Month Visits, respectively. Subjects who report at least a 50% improvement in leg pain will be considered responders.

7.9.2.4.   Analysis Methods

The analysis methods described in this section will be used for all secondary efficacy objectives.

The responder rate as defined for each secondary objective will be calculated for subjects in the Treated Analysis Set. The score (Wilson) method will be used to calculate the 95% confidence interval of the responder rate.

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7.10. Safety Evaluation

7.10.1. Adverse Events and Device Deficiencies

In this study, only device-, therapy- and procedure-related adverse events (AEs) and device deficiencies that occur from enrollment through subject discontinuation from the study will be collected. All AEs and device deficiencies will be summarized.

Adverse events and device deficiencies will be summarized by study phase (e.g., Pre-Trialing, Trialing, Implant), with the appropriate number of corresponding subjects as the denominator within each study phase as described below.

Adverse events and device deficiencies, referred to as "events" within this section, will be summarized separately. Events will be coded and summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). Summaries will be presented as the number of events, the number of serious events (for adverse events only), the number of subjects who experienced the event, and the percent of subjects who experienced the event.

Each event summary will be presented in 2 ways (separate tables) using MedDRA's coding system:

(1) By MedDRA System Organ Class (SOC) and Preferred Term (PT), sorted first by the recommended SOC order, then in descending order within PT by percent of subjects, number of events, number of serious events (for adverse events), and then alphabetically by PT

(2) By MedDRA PT, sorted in descending order by percent of subjects, number of events, number of serious events (for adverse events), and then alphabetically by PT.

Each adverse event is evaluated for whether it qualifies as an Unanticipated Serious Adverse Device Effect (USADE). All USADEs will also be summarized separately by study phase as described below. If no USADEs occur, a statement indicating that will be included.

In addition to the summaries above, device deficiencies may also be summarized by device type and PT.

Detailed listings of all adverse events and device deficiencies will be included in the final study report.

7.10.1.1.   Pre-Trialing Events

Because only device-, therapy-, or procedure-related adverse events and device deficiencies are being collected, it is unlikely that any adverse events will be reported prior to trialing. However, if any adverse events have an onset date on or after enrollment and prior to the Device Trial (Day 0) Visit, they will be summarized as Pre-Trialing Events. The denominator for percent of subjects who experienced the event will be all subjects in the Enrolled Analysis Set.

7.10.1.2.   Trialing Events

Events that have an onset date on or after the Device Trial (Day 0) Visit and either through the Study Exit date or prior to the Implant Visit (whichever date is earlier) will be summarized as Trialing Events. The denominator for percent of subjects who experienced the event will be all subjects in the Trialed Analysis Set.

7.10.1.3.   Post-Implant Events

Events that have an onset date on or after the Implant Visit and prior to the Device Activation Visit will be summarized as Post-Implant Events. The denominator for percent of subjects who experienced the event will be all subjects in the Implanted Analysis Set.

7.10.1.4.   Post-Device Activation Events

Events that have an onset date on or after the Device Activation Visit will be summarized as Post-Device Activation Events. The denominator for percent of subjects who experienced the event will be all subjects in the Treated Analysis Set.

In addition to overall Post Device-Activation event summaries, the subset of events with an onset date prior to the Month 3 Visit will be summarized.

For the purposes of reporting on ClinicalTrials.gov, the following summary tables of Post-Device Activation adverse events will also be created for subjects in the Treated Analysis Set:

(1) All serious adverse events, summarized by MedDRA PT, sorted in descending order by percent of subjects with serious events, number of serious events, and then alphabetically by PT

(2) All non-serious adverse events that occurred in at least 5% of subjects, summarized by MedDRA PT, sorted in descending order by percent of subjects, number of events, and then alphabetically by PT.

7.10.2. Surgical Revisions

System modifications following permanent system implant will be presented. Device modifications that occur between system implant and device activation will be summarized separately from the device modifications that occur after device activation. Summaries will include the device component(s) modified, the type of modification (explant, replacement, repositioning), and the primary reason for modification (adverse event, device deficiency, other). The percent of subjects with at least 1 device surgical revision will be summarized.

7.11. Changes to Planned Analysis

Any deviations from this SAP will be described and justified in the final study report, as appropriate.

8. Validation Requirements

Statistical programming code that affects the result of the main analysis (e.g., not including sensitivity or supporting analyses) for the primary objective shall be validated using Level I validation. Programming code that affects the result of the main analysis for the secondary objectives shall be validated at least using Level II validation. In addition, those main statistical analyses that are planned for publication and have not been previously validated should be validated with at least Level II validation. Level III validation may be used for any previously validated program where only minor/administrative changes were made (eg, change the location of the data directory). Additional measures may need to be validated as determined by statistical management.

9. References