Official Title:
Statistical Analysis Plan (SAP): Treatment of Post-Operative Pain Following Orthopedic Surgery with SPRINT® Peripheral Nerve Stimulation (PNS) System in a Randomized, Double-Blinded, Placebo-Controlled Trial

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Statistical Analysis Plan (SAP)

Treatment of Post-Operative Pain Following Orthopedic Surgery with SPRINT® Peripheral Nerve Stimulation (PNS) System in a Randomized, Double-Blinded, Placebo-Controlled Trial

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1.0 Version Control

This Statistical Analysis Plan (SAP) is based on study protocol [redacted].

2.0 Objectives

The study objective is to gather post-market data regarding the safety and effectiveness of the peripheral nerve stimulation (PNS) therapy for the treatment of postoperative pain following knee replacement.

3.0 Study Design

The current study is a prospective randomized, double-blinded, placebo-controlled, multicenter study to gather data regarding the treatment of postoperative pain following orthopedic surgery (e.g., total knee replacement [TKR] and partial/unicompartmental knee replacement [PKR]; including unilateral and bilateral knee replacements and primary and revision knee replacements) with the PNS therapy. Details on study design can be found in the study protocol (0150-CSP-000).

3.1 Randomization

Qualifying individuals will be randomized to either Group #1 (Treatment) or Group #2 (Control) using permuted-block randomization. Eligibility and the schedule and procedure for randomization are detailed in the study protocol (0150-CSP-000). [redacted] Subjects included in the primary endpoint analysis (subjects who have undergone a primary TKR) will be randomized separately from subjects in the exploratory analysis group (subjects who have undergone a PKR or secondary/revision TKR) to maintain an appropriate distribution for the primary endpoint analysis. Individuals will be blinded to their randomization assignment until the close of Visit 11 (3-mo after start of therapy). [redacted]

3.2 Sample Size Rationale

[redacted]

[redacted]

4.0 Study Hypotheses

The primary hypothesis is tested under a significance level of 0.05 (two-sided). All secondary hypotheses are considered exploratory in nature and claims of statistical significance will not be made based on the statistical tests. Any hypotheses tested will be at a significance level of 0.05 (two-sided) with no adjustments for multiple comparisons. Primary, secondary, and exploratory endpoints are described in Section 5.0 (Endpoint Analyses) and Section 8.0 (Efficacy Analyses), including the data collection instruments, data analysis techniques (*e.g.*, thresholds for success in a given outcome), and statistical tests for each endpoint.

4.1 Primary Hypothesis

Overall Proportion of Success in Group #1 (G1) with active PNS vs. Group #2 (G2) with sham PNS for reduction of postoperative pain following a primary total knee replacement orthopedic surgery. The null (H_0) and alternative hypotheses (H_a) are:

H_0: $p_{G1} - p_{G2} = 0$ vs.

H_a: $p_{G1} - p_{G2} \neq 0$

where **p_{G1}** and **p_{G2}** are the **proportions of success** in **average pain intensity** during **Weeks 5-8** in active PNS Group #1 and sham PNS Group #2, respectively.

4.2 Secondary Hypotheses

The Secondary null (H_0) and alternative hypotheses (H_a) are:

1) Proportions of success in average pain intensity between groups for Weeks 1-4. The null (H_0) and alternative hypotheses (H_a) are:

   H_0: $p_{G1} - p_{G2} = 0$ vs.

   H_a: $p_{G1} - p_{G2} \neq 0$

   where **p_{G1}** and **p_{G2}** are the **proportions of success** for **average pain intensity** during **Weeks 1-4** in Group #1 and during **Weeks 1-4** in Group #2, respectively.

2) Proportions of success in average pain intensity (durability of primary endpoint) at 3, 6, 9, and 12 months after SOT

   H_0: $p_{G1} - p_{G2} = 0$ vs.

   H_a: $p_{G1} - p_{G2} \neq 0$

   where **p_{G1}** and **p_{G2}** are the **proportions of success** for **average pain intensity** at **follow up (3, 6, 9, and 12 months after SOT** in Group #1 and **3 months after SOT** in Group #2).

3) Mean average pain relief at specified intervals after start of therapy

   H_0: $u_{G1} - u_{G2} = 0$ vs.

   H_a: $u_{G1} - u_{G2} \neq 0$

   where **u_{G1}** and **u_{G2}** are the **mean percent improvement** in **average pain intensity** at **specified intervals after start of therapy (Weeks 1-4, Weeks 5-8, and 3, 6, 9, and 12**

months after SOT in Group #1 and **Weeks 1-4, Weeks 5-8, and 3 months after SOT** in Group #2).

4) Pain medication usage at specified intervals after start of therapy (opioid, non-opioid and total analgesic medication usage analyzed separately)

   H_0: $p_{G1} - p_{G2} = 0$ vs.

   H_a: $p_{G1} - p_{G2} \neq 0$

   where **p_{G1}** and **p_{G2}** are the **distribution probabilities** for **pain medication usage** at **monthly intervals (Weeks 1-4, Weeks 5-8, and 3, 6, 9, and 12 months after SOT** in Group #1 and **Weeks 1-4, Weeks 5-8, and 3 months after SOT** in Group #2).

5) Pain Catastrophizing Scale (PCS) at specified intervals after start of therapy

   H_0: $u_{G1} - u_{G2} = 0$ vs.

   H_a: $u_{G1} - u_{G2} \neq 0$

   where **u_{G1}** and **u_{G2}** are the **mean percent improvement** in **PCS** at **specified intervals after start of therapy (4 weeks, 8 weeks after SOT** in Group #1 and **4 weeks, 8 weeks after SOT** in Group #2).

6) Patient global impression of change (PGIC) at specified intervals after start of therapy

   H_0: $u_{G1} - u_{G2} = 0$ vs.

   H_a: $u_{G1} - u_{G2} \neq 0$

   where **u_{G1}** and **u_{G2}** are the **mean scores** for **PGIC** at **specified intervals after start of therapy (4 weeks, 8 weeks, and 3, 6, and 12 months after SOT** in Group #1 and **4 weeks, 8 weeks, and 3 months after SOT** in Group #2).

7) Pain Interference (BPI-9) at specified intervals after start of therapy

   H_0: $p_{G1} - p_{G2} = 0$ vs.

   H_a: $p_{G1} - p_{G2} \neq 0$

   where **p_{G1}** and **p_{G2}** are the **proportions of success** for **pain interference** at **specified intervals after start of therapy (4 weeks, 8 weeks, and 3, 6, 9, and 12 months after SOT** in Group #1 and **4 weeks, 8 weeks, and 3 months after SOT** in Group #2).

8) Physical recovery (Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC) at specified intervals after start of therapy

   H_0: $p_{G1} - p_{G2} = 0$ vs.

   H_a: $p_{G1} - p_{G2} \neq 0$

   where **p_{G1}** and **p_{G2}** are the **proportions of success** for WOMAC at **specified intervals after start of therapy (8 weeks, and 3, 6, and 12 months after SOT** in Group #1 and **8 weeks and 3 months after SOT** in Group #2).

9) 6MWT at specified intervals after start of therapy

   H0: $u_{G1} - u_{G2} = 0$ vs.

   Ha: $u_{G1} - u_{G2} \neq 0$

   where **u_{G1}** and **u_{G2}** are the **mean percent improvement** on the 6MWT at **specified intervals after start of therapy (8 weeks and 3 months after SOT).**

5.0 Endpoint Analyses

Analyses of the primary and secondary effectiveness endpoints will be conducted on the full analysis set and the per-protocol population set at each specified study interval. The full analysis

set is considered the primary population for formal statistical hypothesis testing. [redacted]

5.1 Primary Endpoint

Relief of postoperative pain will be evaluated using the average pain intensity. All subjects will record pain scores daily for the qualifying knee (*i.e.,* with total knee implant and qualifying pain) in the 7-day diaries using BPI-SF Question #5. Data will be collected [redacted]. Each subject must have ≥50% reduction in pain relative to baseline to be considered a success in the primary efficacy endpoint analysis. Missing data [redacted] will be handled according to Section 8.2. The primary endpoint analysis will be based upon the Full Analysis Set, including imputation for missing data due to missed visits and early termination. An analysis will also be performed based on the Per Protocol population, [redacted] Group #1 will receive active stimulation and Group #2 will receive sham stimulation during the 8-week home trial. [redacted]

The primary endpoint compares the proportion of subjects in Group #1 relative to that in Group #2 that achieve ≥ 50% reduction in pain from baseline to Weeks 5-8 of the home trial using a Fisher's exact test. The null hypothesis (H_0) is that the PNS treatment (Group #1, active stimulation) is equal to the control (Group #2, sham stimulation) in providing pain relief. The alternative hypothesis (H_a) is that Group #1 has a proportion of successes that is not equal to the proportion of successes in Group #2.

H_0: proportion of successes in Group #1 = proportion of successes in Group #2
H_a: proportion of successes in Group #1 ≠ proportion of successes in Group #2

If the proportion of successes in the PNS treatment is larger than the proportion of successes in the control during the Weeks 5-8 of the home trial and statistically significantly different ($p < 0.05$, two-sided), then the null hypothesis is rejected at the 0.05 level of significance, which will indicate that the therapeutic effect is clinically significant and superior to the placebo effect[2]. [redacted]

[redacted] Additional analyses may be performed to assess treatment effect for time from TKR.

5.2 Secondary Endpoints

5.2.1 Proportions of success in average pain intensity during Weeks 1-4 of home trial

The proportion of subjects who successfully achieve ≥ 50% reduction from baseline in Group #1 during Weeks 1-4 of the 8-week home trial will be compared to that in Group #2 during Weeks 1-4 of the sham period using a Fisher's exact test. The pain intensity scores will be determined for each subject by applying the same method used for the primary endpoint: taking the mean of the daily average pain intensity (BPI-SF Question #5) reported in the 7-day diary at baseline compared to the mean score for the same regions of pain reported over Weeks 1-4 of treatment (*i.e.*, the average of all scores in the diaries during this period) for Group #1 and Group #2. To be considered a success, subjects must have ≥ 50% reduction in pain. The null hypothesis is that there is no difference in the proportions of success between the two treatment groups, versus the alternative hypothesis, that the proportions of success differ from one another. Testing will be conducted at the 0.05 level of significance. [redacted]

5.2.2 Long-term Durability of Pain Relief at 3, 6, 9, and 12 months after SOT

The analysis of the durability of the treatment effect on average pain intensity will be conducted at 3, 6, 9, and 12 months after the start of therapy by comparing the proportion of subjects who successfully achieve ≥ 50% reduction from baseline in Group #1 at each time point compared to 3 months after the start of therapy (the longest follow-up before crossover) in Group #2 using a Fisher's exact test. The pain intensity scores will be determined for each subject by applying the same method used for the primary endpoint: taking the mean of the daily average pain intensity (BPI-SF Question #5) reported in the 7-day diary at baseline compared to the mean score reported in the follow-up diary (*i.e.*, 3, 6, 9, or 12 months after SOT for Group #1; compared to 3 months after SOT in Group #2). To be considered a success, subjects must have ≥ 50% reduction in pain. The null hypothesis is that there is no difference in the proportions of success between the two treatment groups, versus the alternative hypothesis, that the proportions of success differ from one another. Testing will be conducted at the 0.05 level of significance. [redacted]

5.2.3 Mean pain relief for Weeks 1-4, Weeks 5-8, and 3, 6, 9, and 12 months after SOT

The analysis of treatment effect on average pain compares the mean percent improvement from baseline to the specified intervals after start of therapy. The mean percent improvement in Group #1 for Weeks 1-4, Weeks 5-8, and 3 months will be compared to Group #2 for Weeks 1-4, Weeks 5-8, and 3 months, respectively. The mean percent improvement in Group #1 at 6, 9, and 12 months will be compared to Group #2 at 3 months (the longest follow-up before crossover). A two-sided Wilcoxon rank-sum test will be performed to assess the difference between groups.

During the home trial (*i.e.*, Weeks 1-4 or Weeks 5-8 of the home trial), the average pain intensity scores will be determined for each subject by taking the mean of the daily average (BPI-SF Question #5) reported in the 7-day diary at baseline compared to the mean score for in the 7-day diaries during Weeks 1-4 or Weeks 5-8 of the home trial, respectively [redacted]

[redacted]. Similarly, at 3, 6, 9, or 12 months after start of therapy, the mean average pain intensity scores will be determined by taking the mean of the daily average pain (BPI-SF Question #5) reported in the 7-day diary at baseline compared to the mean pain score in the 7-day diaries preceding each visit [redacted]. The null hypothesis is that the distribution of mean change in average scores is the same for the two groups; the alternative hypothesis is that one of the distributions is shifted relative to the other distribution by a constant amount. Testing will be conducted at the 0.05 level of significance. [redacted]

5.2.4 Pain Medication Usage at 4 weeks, 8 weeks, and 3, 6, 9, and 12 months after SOT

1) Pain medication usage between groups

The analysis of pain medication usage examines changes in medication usage between the two groups. Changes in medication will be reviewed for Weeks 1-4 of therapy, Weeks 5-8 of therapy, and at 3, 6, and 12 months after the start of therapy. For this analysis, a blinded third-party medication committee will review medications of study participants collected for each diary collection period and will use the following convention for scoring medication changes, in comparison to the baseline diary medications:

- **No change** = No change in dosage or change is not clinically meaningful to impact pain outcomes.
- **Increase** = Clinically meaningful increase in medication that would impact pain outcomes.
- **Decrease** = Clinically meaningful decrease in medication that would impact pain outcomes.

The blinded third-party medication committee (comprised of three clinicians experienced in the treatment and management of pain) will serve as the evaluator for all clinical sites. Final determinations of changes in medication usage will require agreement among at least two of the three blinded evaluators. In cases where there is 1:1:1 tie, the medication review committee will convene to discuss and adjudicate the final determination.

The distribution of changes in opioid pain medication usage (decrease/no change/increase) will be reported first using an exact Mantel-Haenszel test to compare the ordered distributional responses (percentage of subjects within each category) between Group #1 and Group #2. Group #1 at Weeks 1-4, Weeks 5-8, and 3 months will be compared to Group #2 at Weeks 1-4, Weeks 5-8, and 3 months, respectively. Group #1 at 6, 9, and 12 months will be compared to Group #2 at 3 months (the longest follow-up before crossover). Assuming there is a statistically significant difference in the ordered distributional responses between Group #1 and Group #2 at a given timepoint, a subsequent statistical test will be carried out to compare between groups the percent of subjects categorized as having a decrease in opioid pain medication. In addition to opioids, this analysis will also be repeated for analysis of all pain medications, and non-opioid analgesic usage independently.

The null hypothesis is that the difference in the proportion of subjects categorized as "decrease in pain medication" between the treatment and control groups is not statistically significant. The alternative hypothesis is that the difference in the proportion of subjects categorized as "decrease in pain medication" is statistically significant at the 0.05 significance level.

[redacted]

2) Effect of pain medication on reductions in postoperative pain

The effect of change in medication will also be examined using logistic regression with patient outcome at the primary endpoint (success/failure) as the dependent variable and two binary independent variables, one which indicates treatment, and the other which serves as a potential explanatory (independent) variable for change in medication defined as follows: increase in overall medication use versus no change/decrease. Changes in medication will be reviewed for Weeks 1-4 of therapy, Weeks 5-8 of therapy, and at 3 months after the start of therapy in Group #1 and Group #2, and at 6, 9, and 12 months after the start of therapy in Group #1. The purpose of the analysis is to determine whether changes in medication are a statistically significant predictor of success above and beyond the therapeutic effect (*i.e.* evaluated as a covariate) and will not affect the results of the primary endpoint. A blinded third-party medication committee will review medications of study participants collected for each diary collection period and will use the following convention for scoring medication changes, in comparison to the baseline diary medications:

- **No change** = No change in dosage or change is not clinically meaningful to impact pain outcomes.
- **Increase** = Clinically meaningful increase in medication that would impact pain outcomes.
- **Decrease** = Clinically meaningful decrease in medication that would impact pain outcomes.

The blinded third-party medication committee (three clinicians experienced in the treatment and management of pain) will serve all clinical sites. Final determinations require agreement among at least two of the three blinded medication evaluators. In cases where there is a 1:1:1 tie, the medication review committee will convene to discuss and adjudicate the final determination.

This analysis will be conducted for opioids, then repeated for analysis of all pain medications, and then non-opioid analgesic usage independently.

5.2.5 Pain Catastrophizing Scale (PCS) at 4 weeks and 8 weeks after SOT

PCS is a widely-used, validated 13-question instrument to assess rumination (4 questions), magnification (3 questions), and helplessness (6 questions). The survey asks participants to think back on painful experiences in the past and reflect on how often they had specific thoughts or feelings. Each question is scored on a 0-4 scale with 0 = "not at all" and 4 = "all the time". Higher scores indicate a greater tendency towards catastrophizing pain, which has been correlated with worse pain and response to pain therapies.

The analysis of treatment effect on PCS examines the difference in the mean percent improvement from baseline at specified intervals in Group #1 relative to that of Group #2. The baseline PCS score will be compared to the PCS score at the specified intervals after start of therapy. The mean percent improvement in Group #1 at 4 weeks and 8 weeks will be compared to

Group #2 at 4 weeks and 8 weeks, respectively. The difference between groups will be evaluated with a Wilcoxon rank-sum test. The null hypothesis is that there is no difference in mean percent improvement between the two treatment groups, versus the alternative hypothesis, that the mean percent improvements differ from one another. Testing will be conducted at the 0.05 level of significance.

5.2.6 Patient Global Impression of Change at 4 weeks, 8 weeks, and 3, 6, 9, and 12 months after SOT

The analysis of treatment effect on the PGIC compares the rank scores (of 7 possible ranks, ranging from -3 to 0 to +3, where -3 is very much worse, 0 is no change, and +3 is very much improved) of Group #1 to Group #2. The mean rank score of Group #1 at 4 weeks, 8 weeks, and 3 months will be compared to Group #2 at 4 weeks, 8 weeks, and 3 months, respectively. The mean rank score of Group #1 at 3, 6, and 12 months will be compared to Group #2 at 3 months (the longest follow-up before crossover). The difference between groups will be evaluated with a Wilcoxon rank-sum test. The null hypothesis is that there is no difference in the mean rank score between the two treatment groups, versus the alternative hypothesis, that the mean rank scores differ from one another. Testing will be conducted at the 0.05 level of significance. [redacted]

5.2.7 Pain Interference at 8 weeks, and 3, 6, 9, and 12 months after SOT

The analysis of the treatment effect on pain interference compares the proportion of subjects who successfully achieve ≥ 50% reduction in average pain interference score in Group #1 at each time point relative to that in Group #2 based on a Fisher's exact test. Relief of pain interference will be evaluated using the average pain interference (BPI-SF Question #9). The baseline average pain interference score will be compared to the average pain interference score at each specified interval after start of therapy to determine the percent reduction in pain interference. To be considered a success, subjects must have ≥ 50% reduction in the average pain interference score. The proportion of success in Group #1 at 4 weeks, 8 weeks, and 3 months will be compared to Group #2 at 4 weeks, 8 weeks, and 3 months, respectively. The proportion of success in Group #1 at 3, 6, and 12 months will be compared to Group #2 at 3 months (the longest follow-up before crossover). The null hypothesis is that there is no difference in proportions of success between the two treatment groups, versus the alternative hypothesis, that the proportions of success differ from one another. Testing will be conducted at the 0.05 level of significance. [redacted]

5.2.8 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 8 weeks, 3, 6, 9, and 12 months after SOT

The analysis of treatment effect on function (*i.e.,* physical recovery) compares the proportion of subjects who successfully achieve ≥ 33% improvement[3-5] in average WOMAC score in Group #1 at each time point relative to that in Group #2 based on a Fisher's exact test. The WOMAC questionnaire assesses physical recovery and includes 24 items assessing pain, stiffness, and difficulty with daily activities. Each item is scored on an 11-point numerical rating scale from 0-10 with lower numbers indicating improved physical recovery, and the total score is calculated.

The WOMAC scores will be collected at baseline and compared to the WOMAC scores at each specified interval after start of therapy to determine the percent improvement (*i.e.,* reduction in score) in physical recovery. To be considered a success, subjects must have ≥ 33% reduction in the WOMAC score. The proportion of success in Group #1 at 8 weeks and 3 months will be compared to Group #2 at 8 weeks and 3 months, respectively. The null hypothesis is that there is no difference in proportions of success between the two treatment groups, versus the alternative hypothesis, that the proportions of success differ from one another. Testing will be conducted at the 0.05 level of significance. [redacted]

5.2.9 Six Minute Walk Test (6MWT) at 8 weeks and 3 months after SOT

The 6MWT measures the distance walked in 6 minutes and will be used to assess walking speed and endurance. Subjects that are unable to complete the 6MWT will be assigned a score of 0 for that visit. The analysis of treatment effect on the 6MWT examines the difference in the mean percent improvement from baseline at specified intervals in Group #1 relative to that of Group #2. The baseline 6MWT score will be compared to the 6MWT score at the specified intervals after start of therapy. The mean percent improvement in Group #1 at 8 weeks and 3 months will be compared to Group #2 at 8 weeks and 3 months, respectively. The difference between groups will be evaluated with a Wilcoxon rank-sum test. The null hypothesis is that there is no difference in mean percent improvement between the two treatment groups, versus the alternative hypothesis, that the mean percent improvements differ from one another. Testing will be conducted at the 0.05 level of significance. [redacted]

5.2.10 Exploratory Analyses

[redacted]

[redacted]

[redacted]

6.0 Analysis Populations

[redacted]

6.2 Full Analysis Set

The Full Analysis Set (using a modified Intent to Treat approach) will include all subjects who sign a consent form, are randomized, and continue to meet eligibility criteria prior to the time of the lead placement procedure. All patients implanted with at least 1 lead with available data in weeks 5-8 will be analyzed according to the treatment group to which they were randomized.

- Subjects who had a partial knee replacement or a revision knee replacement are excluded

6.3 Per Protocol Set

The per-protocol set of subjects defines a subset of the subjects in the Full Analysis Set who also meet the following criteria:

- Received correct treatment for group to which they were randomized
- Were implanted with two MicroLeads
- Reported [redacted] coverage of [redacted] in the region of postoperative pain during the primary endpoint period (Weeks 5-8) (Group #1 only)
- Not missing more than [redacted] of average pain intensity (BPI-5) scores in the diaries during the primary endpoint period (*i.e.,* Weeks 5-8 of home trial)
- Continued study eligibility throughout treatment period (Weeks 1-8) [redacted]

6.4 Safety Population

The Safety set is based on the Full Analysis Set with the following modifications:

- Subjects will be assessed with an As Treated analysis, with therapeutic group determined by the treatment they actually received.
- Any subjects for whom lead placement is attempted will be included, even if no leads are implanted
- Any subjects for whom treatment is not attempted (*i.e.* no attempted lead placement occurs) will be excluded.

6.5 Exploratory Analysis Population – partial and revision knee replacements

[redacted]

7.0 Subject Disposition and Baseline Information

7.1 Subject Disposition

Study completion and withdrawal details, inclusion and exclusion criteria, randomization, and population assignment will be listed. [redacted]

Table 1. Subject Disposition Categories

Disposition Category	Description
Screened Potential Subjects	All potential subjects who are screened for study participation will be listed on a screening log. Those potential subjects who are excluded will be listed along with the reason for exclusion. Screened potential subjects include those individuals that were screened from record searches.
Consented	Any subject who signs an Informed Consent.
Screen Failures	Any subject who signs an informed consent but does not proceed with randomization will be dispositioned as a screen failure. These subjects will not be counted against allowable site IRB subject totals.
Randomized	Subjects who sign a consent form, meet all eligibility criteria (including a completed baseline diary), and are assigned to a Group will be considered "randomized" in the study. Any subject who has a lead replaced will still only be counted once against total study enrollment.
[redacted]	[redacted]
[redacted]	

Disposition Category	Description
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Withdrawn	Subjects who voluntarily withdraw their study participation after being randomized will be categorized as withdrawn.
Lost to Follow-Up	After documented attempts at contacting the individual, subjects who are unreachable or unresponsive to requests for study visits will be categorized as lost to follow-up.
Terminated	Subjects who are prematurely terminated from the study by the Investigator are categorized as terminated. A Study Exit Form will capture the reason for study termination.
Completed	Subjects who receive one or more leads and complete all applicable follow-up visits are categorized as completed. Group #2 subjects that complete Visit 11 will be considered Completed. Group #2 subjects may choose to be discharged from the study after Visit 11, or cross over to receive stimulation. Subjects may be designated Withdrawn, Lost to Follow-Up, or Terminated during the crossover treatment or crossover follow-up period without impacting their Completed disposition in the placebo period.

7.2 Baseline and Demographic Characteristics

Demographic and baseline disease characteristic data will be listed and summarized for each group using descriptive statistics for continuous variables and tabulated for categorical variables.

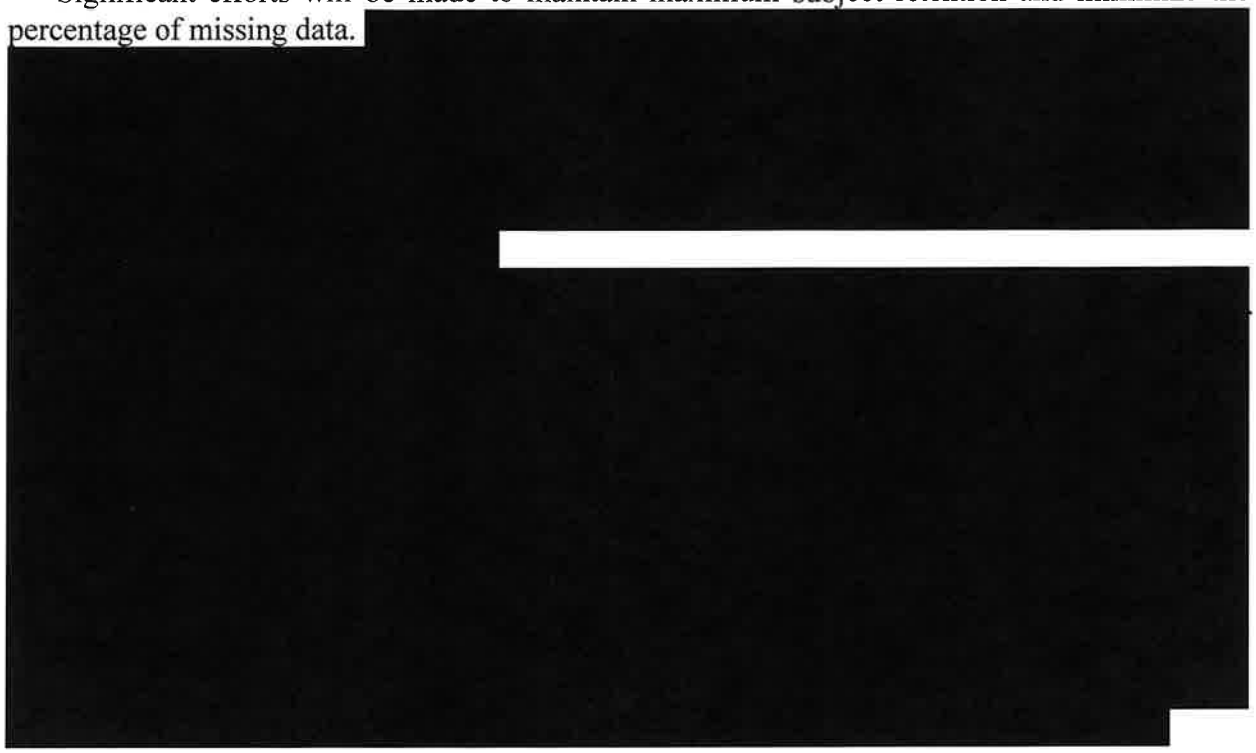
[redacted]

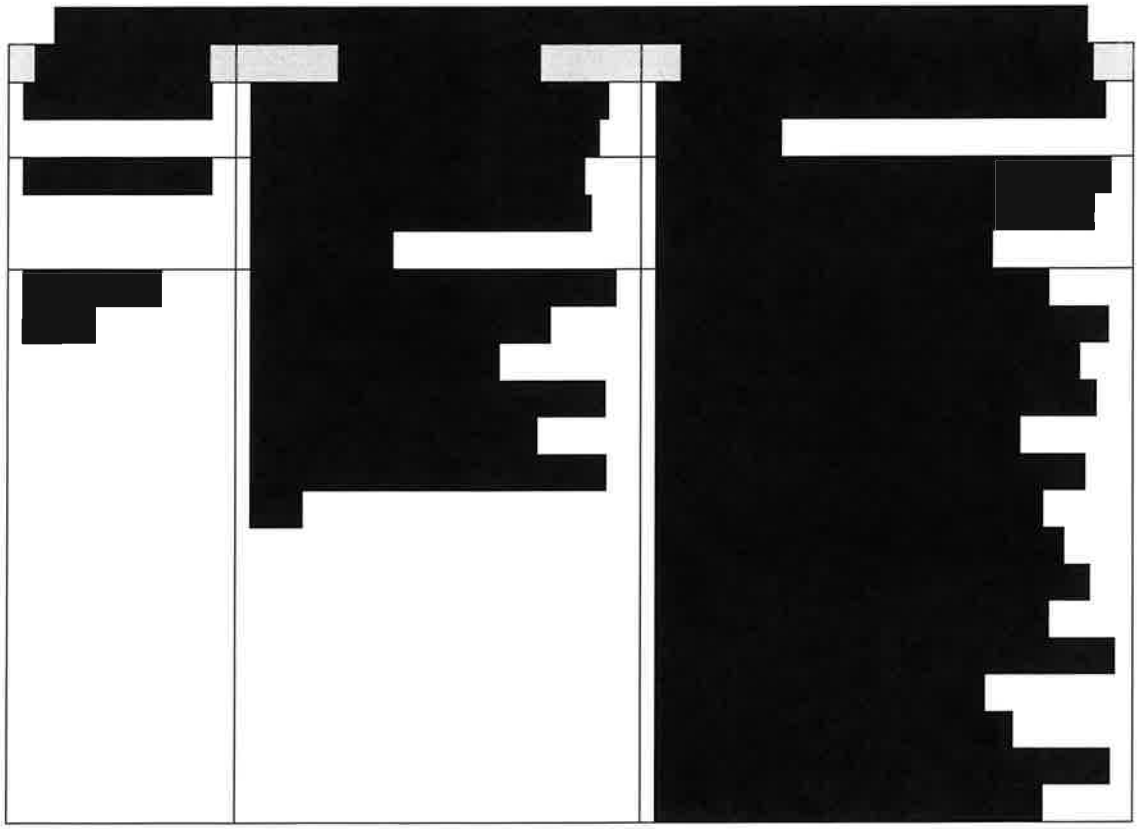
8.0 Additional Data Analysis

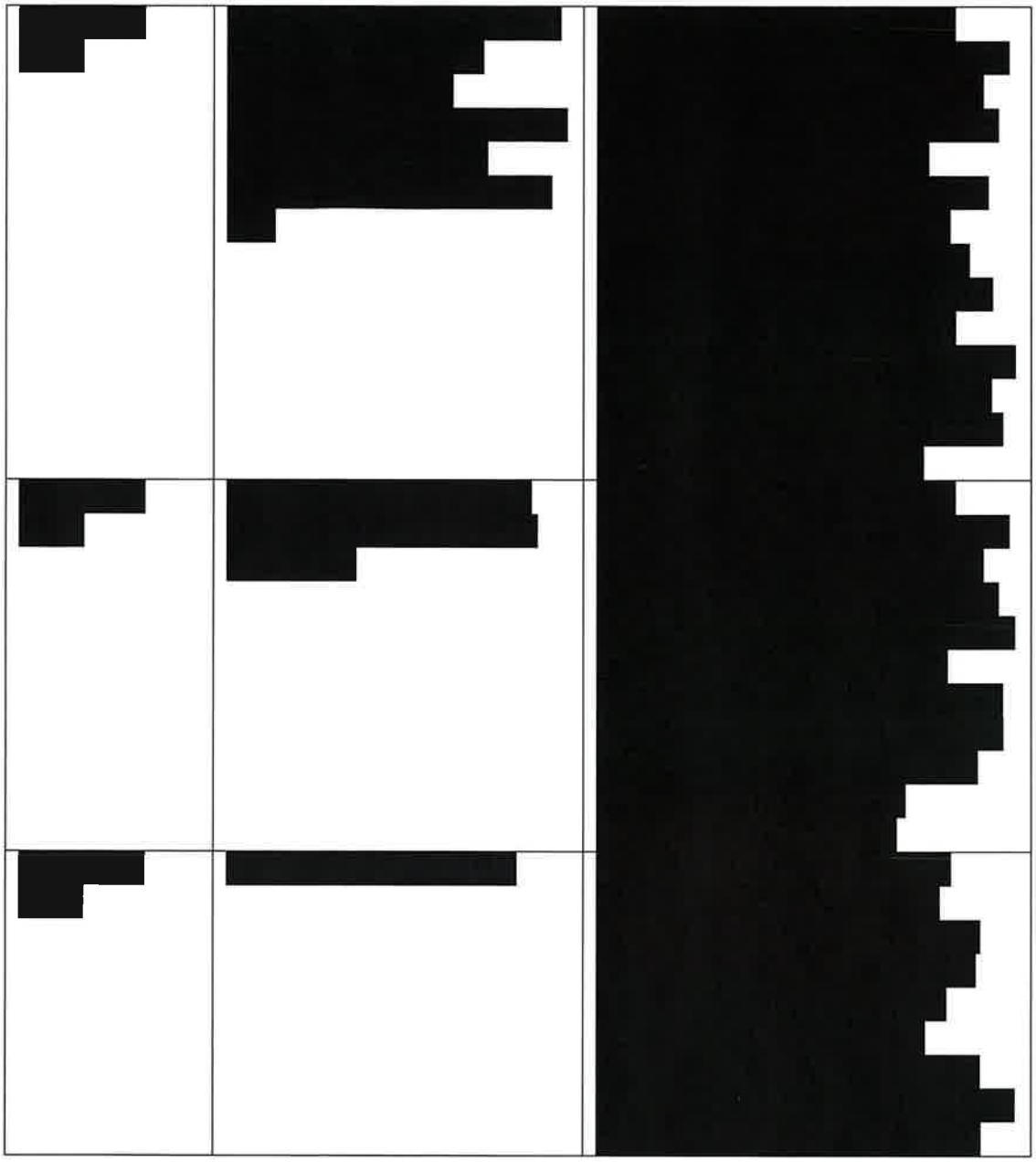
[redacted]

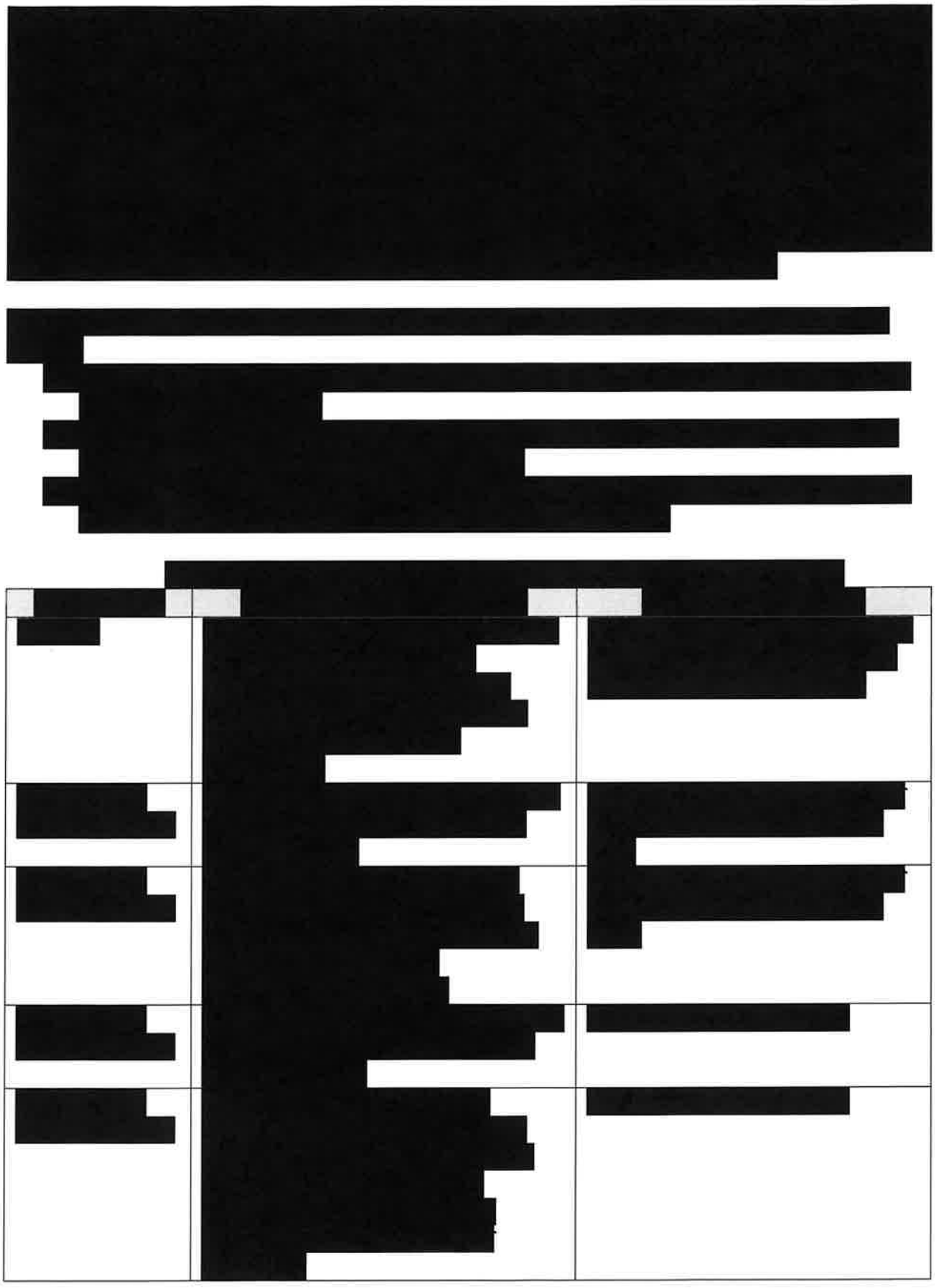
8.2 Handling Missing Data

Significant efforts will be made to maintain maximum subject retention and minimize the percentage of missing data.









[redacted]

9.0 Safety Analysis

All safety data will be analyzed using the Safety Analysis Set. Adverse device effects (ADEs) will be documented, reported, and categorized [redacted]

9.1 Adverse Device Effects

Adverse device effects (ADEs) will be reported and an overall summary of the number and percentage of subjects with at least one ADE, serious ADE, unanticipated ADE, or ADE leading to death will be presented by treatment group. [redacted]