Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE)

NCT02844465

Statistical Analysis Plan

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Medtronic Statistical Analysis Plan	
Clinical Investigation Plan Title	Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE)
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted] Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AED	Anti-Epileptic Drug
[redacted]	[redacted]
ATL	Anterior Temporal Lobectomy
CIP	Clinical Investigation Plan
DMC	Data Monitoring Committee
[redacted]	[redacted]
MTLE	Mesial Temporal Lobe Epilepsy
mITT	Modified Intent to Treat
MRI	Magnetic Resonance Imaging
[redacted]	[redacted]
QOL	Quality of Life
SAP	Statistical Analysis Plan
SLATE	Stereotactic Laser Ablation for Temporal Lobe Epilepsy
SUDEP	Sudden Unexpected Death in Epilepsy
[redacted]	[redacted]

3. Introduction

The purpose of this study is to evaluate the safety and efficacy of the Visualase System for necrotization or coagulation of epileptogenic foci in patients with intractable mesial temporal lobe epilepsy (MTLE). To assess safety, the primary endpoint will measure the incidence of qualifying device-, procedure-, or anesthesia-related adverse events (AEs) through 12 months following the Visualase procedure. To assess efficacy, the primary endpoint will evaluate seizure freedom (defined as Engel Class I) at 12 months following the Visualase procedure.

This is a prospective, single-arm, multicenter, investigational clinical study. The study is expected to be conducted at up to 25 sites located in the United States. A minimum of 150 subjects will undergo the Visualase procedure and be evaluated for a 12-month follow-up. To account for attrition, up to 215 subjects may be enrolled to ensure at least 150 subjects are treated with the Visualase procedure and complete the study requirements.

Following enrollment, subjects' qualification for the Visualase procedure will be confirmed by a central review committee. Baseline assessments will also be performed at any time prior to the Visualase procedure. Study subjects will be followed for 12 months following the Visualase procedure.

The purpose of this statistical analysis plan (SAP) is to provide a comprehensive description, prior to the database lock and data analysis, of the statistical methods and analyses to be used for inclusion in the final study report. Analysis included in the final study report may be used to produce publications per the Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE) Publication Plan. No formal interim analysis is planned. Any interim monitoring of safety data will be conducted under the auspices of a data monitoring committee (DMC) assigned to this study.

The following document was used to create this SAP:

- SLATE Clinical Investigational Plan (CS-05000 Version 4.0, 09 April 2018)

4. Study Objectives and Endpoints

4.1 Study Objective

The study objective is to evaluate the safety and efficacy of the Visualase MRI-Guided Laser Ablation System ("Visualase System") for necrotization or coagulation of epileptogenic foci in patients with intractable MTLE.

4.2 Study Endpoints

One primary safety endpoint, one primary efficacy endpoint, 8 secondary endpoints, [redacted] will be used to evaluate the study objective.

4.2.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of qualifying device-, procedure-, or anesthesia-related adverse events (defined in Appendix 2) through 12 months following the Visualase procedure.

4.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint is seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure.

4.2.3 Secondary Endpoints

1. Seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure compared to historical reference threshold for continued medical therapy
2. Seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure, including subjects who are retreated with Visualase

3. Within-subject change of Boston Naming Test score (English language version), from baseline to 12 months following the Visualase procedure
4. Within-subject change of Rey Auditory Verbal Learning Test 5-Trial Total score (English language version), from baseline to 12 months following the Visualase procedure
5. Within-subject change of Quality of Life in Epilepsy inventory (QOLIE-31) score (English language version), from baseline to 12 months following the Visualase procedure
6. Within-subject change of SF-36 quality of life questionnaire Mental Component Score (English language version), from baseline to 12 months following the Visualase procedure
7. Within-subject change of SF-36 quality of life questionnaire Physical Component Score (English language version), from baseline to 12 months following the Visualase procedure
8. Seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure compared to historical reference threshold for open surgical resection

[redacted]

5. Investigation Plan

This is a prospective, single-arm, multicenter, investigational clinical study. Following informed consent, subjects' qualification for the Visualase procedure will be confirmed by a central review committee (Pre-Surgical Evaluation). Baseline assessments will also be performed at any time prior to the Visualase procedure.

Subjects will then undergo MRI-guided laser ablation of the amygdala and hippocampus with the Visualase System. Subjects will be followed for 12 months following the Visualase procedure and assessed for adverse events, seizures, neuropsychological outcomes, mood, and quality of life outcomes. Figure 1 below illustrates the study design.

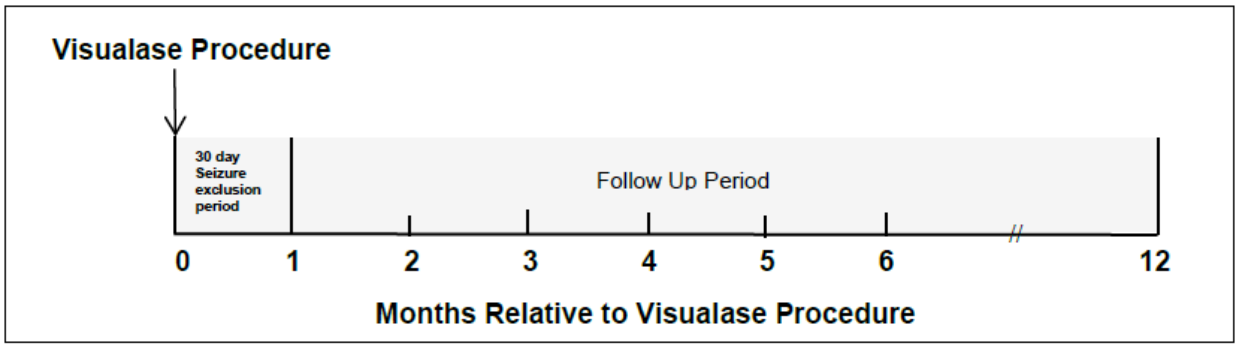


Figure 1. SLATE Study Design

The study subject population consists of adult patients with medically intractable (per the definition by the International League Against Epilepsy (Kwan 2010) MTLE, with radiological and electrophysiological evidence consistent with unilateral focal seizure onsets. A full listing of inclusion and exclusion criteria is contained within the SLATE Clinical Investigational Plan (CIP).

Reference rates taken from the literature will serve as expected safety and efficacy rate for the primary endpoint. Attiah *et al.* (2014) published a decision analysis to calculate the seizure freedom rate and late mortality/morbidity rate that laser ablation for temporal lobe epilepsy would need to demonstrate to provide quality of life (QOL) improvements equivalent to anterior temporal lobectomy (ATL). The meta-analysis included records of over 25,000 cases of ATL and the available data for laser ablation from a recent multicenter study. The results of the analysis revealed that subjects achieving 43% Engel I

outcomes and no more than 40% late mortality/morbidity with laser ablation is needed in order to be grossly equivalent (as defined by the author) to ATL. Therefore, this study compares safety and efficacy outcomes of laser ablation to the 43% seizure freedom and 40% qualifying AE rate threshold of gross equivalence determined by Attiah *et al*. (2014).

Seizure control is expected to yield improvements in health-related quality of life. Primary and secondary endpoints of this study have been designed to evaluate these outcomes. Additional secondary endpoints have been designed to further evaluate the cognitive outcomes after the Visualase procedure.

The study design is limited by the absence of an active control arm. Refer to section 3.2 of CIP.

6. Determination of Sample Size

The primary efficacy endpoint is the 12-month seizure-free rate. The analysis of the primary efficacy endpoint will compare the lower 2-sided exact 95% confidence interval (CI) boundary of the observed rate against 43%. The lower bound of the seizure freedom rate CI following the Visualase procedure must exceed 43%. Based on published and unpublished accounts of seizure freedom rates following laser ablation for MTLE, it is expected that approximately 56% of subjects who undergo the Visualase procedure will be seizure free through 12 months post-procedure. Given the assumption of a 56% success rate with Visualase, 89% power can be achieved with 150 treated subjects to show that the success rate after Visualase is superior to 43%.

Subjects will be considered enrolled upon the signing of a consent form. It is anticipated that once enrolled, some subjects will not proceed to the Visualase procedure due to failure at their pre-surgical evaluation, changes in clinical status, or non-compliance to protocol. Based on these factors, and on previous reports of attrition in similar studies, the assumed attrition rate is 30%. To account for this attrition, up to 215 subjects may be enrolled to ensure at least 150 subjects are treated with the Visualase procedure.

Certain secondary endpoint assessments will be made using subject questionnaires. These self-reported instruments are influenced by primary language. Validated translations are not available in all languages; thus, enrollment will be limited to subjects who can complete these assessments in either English or Spanish. Further, the impact of grouping across translations for analysis is an important consideration. Therefore, for the specified secondary cognitive and QOL endpoints, the subset of only the English-language versions will be used for analysis. To preserve adequate statistical power for analysis of this subset, the total Spanish language enrollment will be restricted to no more than 40% of the total study-wide enrollment population. A 40% cap was chosen based on a conservative assumption that only 73% of subject data are usable, resulting in an evaluable sample of N=109. If only 50% of this sample were used for secondary endpoints restricted to English language (N=55), the power to detect a change in the neuropsychological assessments would be 86%, based on best-estimate effect size.

7. General Statistical Considerations

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition throughout the course of the study will be summarized using a flow chart (e.g., CONSORT flow diagram).

[redacted]

7.1.3 Analysis Sets

The following Analysis Sets ("populations") will be used for analysis of SLATE data.

7.1.3.1 Safety Population

All subjects who sign a consent form (i.e., are enrolled) will be included in the safety population. [redacted] All summaries of safety data will be based on the safety population.

7.1.3.2 Modified Intent to Treat (mITT) Population

All subjects who enter the operating room and start the Visualase procedure (i.e., undergo scalp incision) will be included in the mITT analysis population. The mITT population will be the primary analysis population for efficacy evaluations.

[redacted]

Non-compliance is defined as any subjects who have not submitted enough seizure diaries or qualifiers in their seizure diaries through 12 months, from which the Engel I Classification could not be determined at study exit because of the missing information. The detail of the seizure diaries refers to section 7.5.1 of CIP.

7.2 General Statistical Methods

Statistical analyses will be performed using SAS Software, Version 9.4 or later. Continuous variables will be summarized by N, mean, standard deviation, median, quartile1 and quartile3, minimum, and maximum. Categorical variables will be described by number and percentage. For binary endpoints, a 95% exact CI will be provided.

All statistical tests will be conducted at a two-sided alpha level of 0.05, unless otherwise stated.

This SAP includes a comprehensive description of the statistical methods and reports to be included in the final study report.

7.3 Center Pooling

This study may include up to 25 US centers. Data from all the centers will be pooled. For each tested study endpoint, center effect will not be considered in the statistical modeling. Center-specific analyses are considered to be post hoc and exploratory.

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

7.4.1 Missing Data

Missing primary efficacy endpoint values and missing secondary endpoint values associated with testable hypotheses will be imputed for analysis with the mITT analysis population. Missing primary efficacy endpoint data will be imputed as a binary outcome of seizure freedom, regardless of missing pattern. No daily level imputation will be conducted.

The primary method of imputation will be multiple imputation (SAS PROC MI followed by MIANALIZE). Ten repetitions will be performed and, if needed, will be increased until the algorithm converges. [redacted] The Markov chain Monte Carlo (MCMC) method or Fully Conditional Specification (FCS) will be used with the default number of burn-in iterations before the imputation. The model variables will include: age, sex, race (white, African American, or other), and duration of disease.

[redacted]

[redacted]

7.4.3 Subject Death

Subject death will be treated the same as lost to follow-up, including imputation of missing data. The notable exception is the binary primary efficacy endpoint for seizure freedom: If a subject death after the Visualase procedure has been determined to be seizure-related via the Adverse Event reporting process, the subject may not be imputed as seizure free. Note that Sudden Unexpected Death in Epilepsy (SUDEP) may or may not be seizure-related.

7.5 Adjustments for Multiple Comparisons

Secondary endpoints will be tested only if the primary efficacy endpoint is significant. Secondary endpoints will be tested in a hierarchical fashion to preserve alpha. Each secondary endpoint will be tested at alpha 0.05, but testing will stop when any secondary endpoint fails to achieve significance.

Secondary Endpoints #1, 2 and 8 are not truly independent secondary endpoints; rather they are secondary analyses of the primary efficacy endpoint. To maintain the hierarchical approach for testing the hypotheses and for consistency with the Clinical Investigational Plan, these secondary analyses of the primary endpoint are considered secondary endpoints in this section.

7.6 Demographic and Other Baseline Characteristics

Subject demographics and baseline characteristics; including epilepsy diagnosis, seizure frequency, and other medical history; will be summarized using descriptive statistics for each of the analysis populations.

[redacted]

7.8 Interim Analyses

No formal interim analysis is planned. Any unplanned interim analyses will be conducted under the auspices of the data monitoring committee (DMC) assigned to this study. The DMC is authorized to review interim efficacy and safety analyses and, if necessary, to ensure patient safety, to release results on an as-needed basis to the Medtronic SLATE study team and participating investigators. The DMC will make a recommendation to continue, modify, suspend, or discontinue the study if necessary, to ensure

patient safety. Any such release will be documented and described in the final study report. Study sites will not receive interim results unless they need to know for the safety of their patients.

7.9 Evaluation of Objectives

7.9.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of qualifying device-, procedure-, or anesthesia-related adverse events (defined in Appendix 2) through 12 months following the Visualase procedure.

7.9.1.1 Hypotheses

It is hypothesized that the upper bound of the 95% CI for the proportion of subjects experiencing any qualifying device-, procedure-, or anesthesia-related adverse events (per Appendix 2) through 12 months following the Visualase procedure will be less than 40%. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: $\pi V \geq 0.4$

Alternate Hypothesis: $\pi V < 0.4$

Where πV is the proportion of subjects treated with Visualase experiencing any qualifying AE.

7.9.1.2 Performance Requirements

The criteria of an AE rate of 40% is based on the analysis by Attiah *et al.* (2014). Refer to CIP Section 3.2 for details.

7.9.1.3 Analysis Methods

An exact 95% CI (Clopper 1934) will be calculated to determine if the upper bound of the CI for qualified AEs is less than 40%.

7.9.2 Primary Efficacy Endpoint

The primary efficacy endpoint is seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure (starting at 30 days post-procedure through 365 days post-procedure, to align with Engel Class I definition).

7.9.2.1 Hypotheses

It is hypothesized that the lower bound of the 95% CI for seizure freedom at 12 months following the Visualase procedure will be greater than 43%. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: $\pi V \leq 0.43$

Alternate Hypothesis: $\pi V > 0.43$

Where πV is the proportion of subjects treated with Visualase experiencing no seizures.

An exact 95% CI will be calculated to determine if the lower bound of the CI for seizure freedom at 12 months following the Visualase procedure (πV) will be greater than 43%.

7.9.2.2 Performance Requirements

The performance criterion of seizure-free percentage > 43% is based on the analysis by Attiah *et al.* (2014). Refer to CIP section 3.2 for details.

7.9.2.3 Analysis Methods

An exact 95% CI for the percentage of subjects who are seizure free will be calculated.

7.9.3 Secondary Endpoints

All secondary endpoints have specific hypotheses to be tested. The hypotheses associated with each of these secondary endpoints will be tested in a hierarchical fashion. If the primary efficacy endpoint is not significant, then no secondary endpoints will be tested. Testing of these secondary endpoints will proceed in the following order using an alpha of 0.05 and will stop if any test fails to reach significance.

7.9.3.1 Secondary Endpoint #1

Seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure compared to historical reference threshold for continued medical therapy

It is hypothesized that the seizure freedom at 12 months following the Visualase procedure will be superior to 8% reported in the literature for continued medical therapy (Wiebe 2001). The hypotheses associated with this endpoint are as follows:

Null Hypothesis: $\pi V \leq 8\%$
Alternate Hypothesis: $\pi V > 8\%$

Where πV is the proportion of subjects treated with Visualase experiencing no seizures.

An exact 95% CI for the percentage of subjects who are seizure free will be calculated.

7.9.3.2 Secondary Endpoint #2

Seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure, including subjects who are retreated with Visualase

It is hypothesized that the lower bound of the 95% CI for seizure freedom at 12 months following the Visualase procedure, including subjects retreated with Visualase, will be greater than 43%. Subjects retreated with Visualase will count toward the secondary efficacy endpoint based on their outcome after retreatment. If they have become seizure free and have reached 12 months follow-up from time of retreatment, they are counted as seizure free. Otherwise, they will count as not seizure free. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: $\pi V \leq 0.43$
Alternate Hypothesis: $\pi V > 0.43$

Where πV is the proportion of subjects treated with Visualase experiencing no seizures.

An exact 95% CI will be calculated to determine if the lower bound of the CI for seizure freedom at 12 months (πV) following a subject's last Visualase procedure, including patients retreated with Visualase, will be greater than 43%.

7.9.3.3 Secondary Endpoint #3

Within-subject change of Boston Naming Test score (English language version), from baseline to 12 months following the Visualase procedure

It is hypothesized that the Boston Naming Test score will not decrease from baseline to 12 months following the Visualase procedure. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: μ (V-BNT - BSL-BNT) + $\delta \leq 0$
Alternate Hypothesis: μ (V-BNT - BSL-BNT) + $\delta > 0$

Where μ (V-BNT - BSL-BNT) = mean difference in the Boston Naming Test score from baseline to Month 12 post Visualase.

A non-inferiority test will be performed using a paired t-test, with a non-inferiority delta (δ) of one Reliable Change Index (RCI) of 5 points, to test the hypothesis of no reduction. The 5-point RCI is based on published literature (Sawrie 1996). A two-tailed alpha of 0.05 will be used.

7.9.3.4 Secondary Endpoint #4

Within-subject change of Rey Auditory Verbal Learning Test 5-Trial Total score (English language version), from baseline to 12 months following the Visualase procedure

It is hypothesized that the Rey Auditory Verbal Learning Test 5-Trial Total score will not decrease from baseline to 12 months following the Visualase procedure. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: μ (V-RAVLT - BSL-RAVLT) + $\delta \leq 0$
Alternate Hypothesis: μ (V-RAVLT - BSL-RAVLT) + $\delta > 0$

Where μ (V-RAVLT - BSL-RAVLT) = mean difference in the Rey Auditory Verbal Learning Test 5-Trial Total score from baseline to Month 12 post Visualase.

A non-inferiority test will be performed using a paired t-test, with a non-inferiority delta (δ) of one Reliable Change Index (RCI) of 15 points, to test the hypothesis of no reduction. The 15-point RCI is based on published literature (Sawrie 1996). A two-tailed alpha of 0.05 will be used.

7.9.3.5 Secondary Endpoint #5

Within-subject change of the Quality of Life in Epilepsy inventory (QOLIE-31) score (English language version), from baseline to 12 months following the Visualase procedure, categorized as -1 if the decrease is clinically significant (≤ -11.8), categorized as 0 if not clinically significant (-11.7 to +11.7), and categorized as +1 if the increase is clinically significant (≥ 11.8).

It is hypothesized that the QOLIE-31 score will increase (improve) from baseline to 12 months following the Visualase procedure. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: M (V-QOLIE-31 - BSL-QOLIE-31) ≤ 0
Alternate Hypothesis: M (V-QOLIE-31 - BSL-QOLIE-31) > 0

Where M (V-QOLIE-31 - BSL-QOLIE-31) = sign-test statistic ([increases-decreases]/2) in the Quality of Life in Epilepsy inventory from baseline to Month 12 post Visualase.

A sign test will be used to determine if the median categorical change is significantly greater than zero. The Minimally Clinically Important Difference (MCID) of 11.8 points for the QOLIE-31 is based on published literature (Wiebe 2002).

7.9.3.6 Secondary Endpoint #6

Within-subject change of SF-36 quality of life questionnaire Mental Component Score (English language version), from baseline to 12 months following the Visualase procedure, categorized as -1 if the decrease is clinically significant (≤ -4.58), categorized as 0 if not clinically significant (-4.57 to +4.57), and categorized as +1 if the increase is clinically significant (≥ 4.58).

It is hypothesized that the SF-36 Mental Component Score (MCS) will increase (improve) from baseline to 12 months following the Visualase procedure. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: M (V-SF-36 - BSL-SF-36-MCS) ≤ 0
Alternate Hypothesis: M (V-SF-36 - BSL-SF-36-MCS) > 0

Where M (V- SF-36-MCS - BSL- SF-36-MCS) = sign-test statistic ([increases-decreases]/2) in the SF-36 quality of life questionnaire MCS from baseline to Month 12 post Visualase.

A sign test will be used to determine if the median categorical change is significantly greater than zero. The MCID of 4.58 points for the SF-36-MCS is based on published literature (Wiebe 2002).

7.9.3.7 Secondary Endpoint #7

Within-subject change of SF-36 quality of life questionnaire Physical Component Score (English language version), from baseline to 12 months following the Visualase procedure, categorized as -1 if the decrease is clinically significant (≤ -3.02), categorized as 0 if not clinically significant (-3.01 to +3.01), and categorized as +1 if the increase is clinically significant (≥ 3.02).

It is hypothesized that the SF-36 Physical Component Score (PCS) will increase (improve) from baseline to 12 months following the Visualase procedure. The hypotheses associated with this endpoint are as follows:

Null Hypothesis: $M (V\text{-}SF\text{-}36\text{-}PCS - BSL\text{-}SF\text{-}36\text{-}PCS) \leq 0$
Alternate Hypothesis: $M (V\text{-}SF\text{-}36\text{-}PCS - BSL\text{-}SF\text{-}36\text{-}PCS) > 0$

Where M (V-SF-36-PCS - BSL- SF-36-PCS) = sign-test statistic ([increases-decreases]/2) in the SF-36 quality of life questionnaire PCS from baseline to Month 12 post Visualase.

A sign test will be used to determine if the median categorical change is significantly greater than zero. The MCID of 3.02 points for the SF-36 Physical Component Score is based on published literature (Wiebe 2002).

7.9.3.8 Secondary Endpoint #8

Seizure freedom (defined as Engel Class I, Appendix 1) at 12 months following the Visualase procedure compared to historical reference threshold for open surgical resection

It is hypothesized that the seizure freedom at 12 months following the Visualase procedure will not be inferior to 64% reported in the literature for open surgical resection (Wiebe 2001). The hypotheses associated with this endpoint are as follows:

Null Hypothesis: $\pi V - 64\% + \delta \leq 0$
Alternate Hypothesis: $\pi V - 64\% + \delta > 0$

Where πV is the proportion of subjects treated with Visualase experiencing no seizures.

An exact 95% CI for the percentage of subjects who are seizure free will be calculated and its lower boundary compared to zero after subtraction of the historical open surgical resection percentage of 64% and the addition of the equivalence delta percentage of 10% (Wiebe 2001).

[redacted]

[redacted]

7.10 Safety Evaluation

Adverse events (AEs) will be the primary source of data to evaluate the safety of the procedure. AEs will be coded to Medical Dictionary for Regulatory Activities (MedDRA) terms. The incidence of AEs classified by system organ class and preferred term will be summarized by the number and percentage of subjects with AEs and the number of events will be provided for each category as well. Incidence will report the occurrence (one or more times for a given event for a subject). [redacted]

[redacted]

7.11 Changes to Planned Analysis

As of Version 1.0 of this SAP, there are no changes to planned analysis presented in the CIP. If the data do not warrant a planned analysis, due to such causes as low frequency for an event, the planned analysis will not be performed, but the reason will be explained in the clinical study report.

8. Validation Requirements

The SLATE Clinical Study Management Plan states that Statistical Programming, Quality Control and Validation is a vendor responsibility, and will be conducted according to the vendor's procedures that are consistent with Medtronic SOPs.

9. References

Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069-1077.

Attiah M, Paulo D, Mani R, Danish SF, Stein SC. Anterior temporal lobectomy compared with laser thermal hippocampectomy for mesial temporal epilepsy. Stereotactic Funct Neurosurg 2014;92:15.

Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-413.

Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. New Engl J Med 2001;345:311-318.

Sawrie S, Chelune G, Naugle R, et al. Empirical methods for assessing meaningful neuropsychological change following epilepsy surgery. J Int Neuropsych Soc 1996;2:556-564.

Wiebe S, Matijevic S, Eliasziw M, Derry PA. Clinically Important Change in Quality of Life in Epilepsy. Journal of Neurology Neurosurgery and Psychiatry 2002;73:116-120.

10. Statistical Appendices

The following Appendices are incorporated into this SAP:

a. Appendix 1: Engel Classification of Postoperative Outcome
b. Appendix 2: Qualifying Primary Safety Endpoint Adverse Events

Appendix 1: Engel Classification of Postoperative Outcome[i]

Class I: Free of disabling seizures[a]

A. Completely seizure free since surgery
B. Nondisabling simple partial seizures only since surgery
C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D. Generalized convulsions with AED discontinuation only

Class II: Rare disabling seizures ("almost seizure free")[b]

A. Initially free of disabling seizures but has rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
D. Nocturnal seizures only

Class III: Worthwhile improvement[c]

A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years

Class IV: No worthwhile improvement

A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

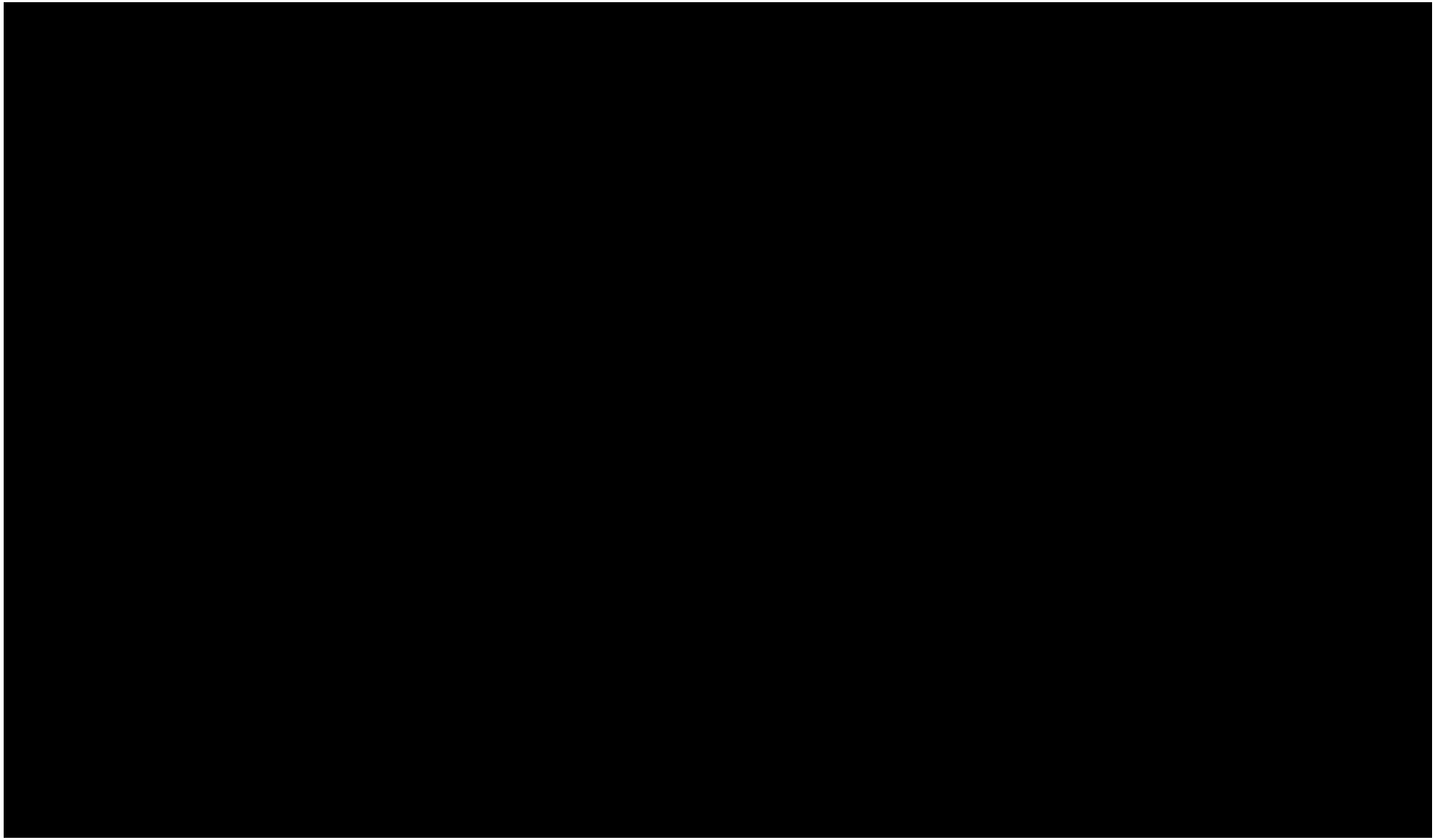
[a]Excludes early postoperative seizures (first few weeks). This exclusion is quantitatively defined as 30 days for this protocol.

[b]"Rare" is quantitatively defined as ≤2 seizure days per year for this protocol.

[c]Determination of "worthwhile improvement" will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and quality of life. This is defined as 80% reduction in seizures for this protocol.

[redacted]

[i]Engel J. Outcome with respect to epileptic seizures. In *Surgical Treatment of the Epilepsies*, edited by J. Engel, Jr. Raven Press, New York. 1987



[redacted]

Appendix 2: Qualifying Primary Safety Endpoint Adverse Events

Adverse events will be reported as specified in the SLATE Clinical Investigational Plan. Study Reportable AEs will count toward the primary safety endpoint if they qualify as follows:

1. Are device-, procedure-, or anesthesia-related; and
2. Are moderate or severe; and
3. Are permanent, for the following adverse events: anxiety, aphasia, blurry vision, depression, diplopia, emotional lability, hemianopia, hemiparesis, memory impairment/difficulty, neurologic deficits, paralysis, psychological/psychiatric complications, quadrantanopia, sensory loss, sleep problems or insomnia

   Note: Transient events were not included in the literature analysis referenced as the performance threshold for the primary safety endpoint.[30]

Figure 3 is a flow-chart to determine if a Study Reportable AE qualifies for inclusion in the primary safety endpoint analysis.

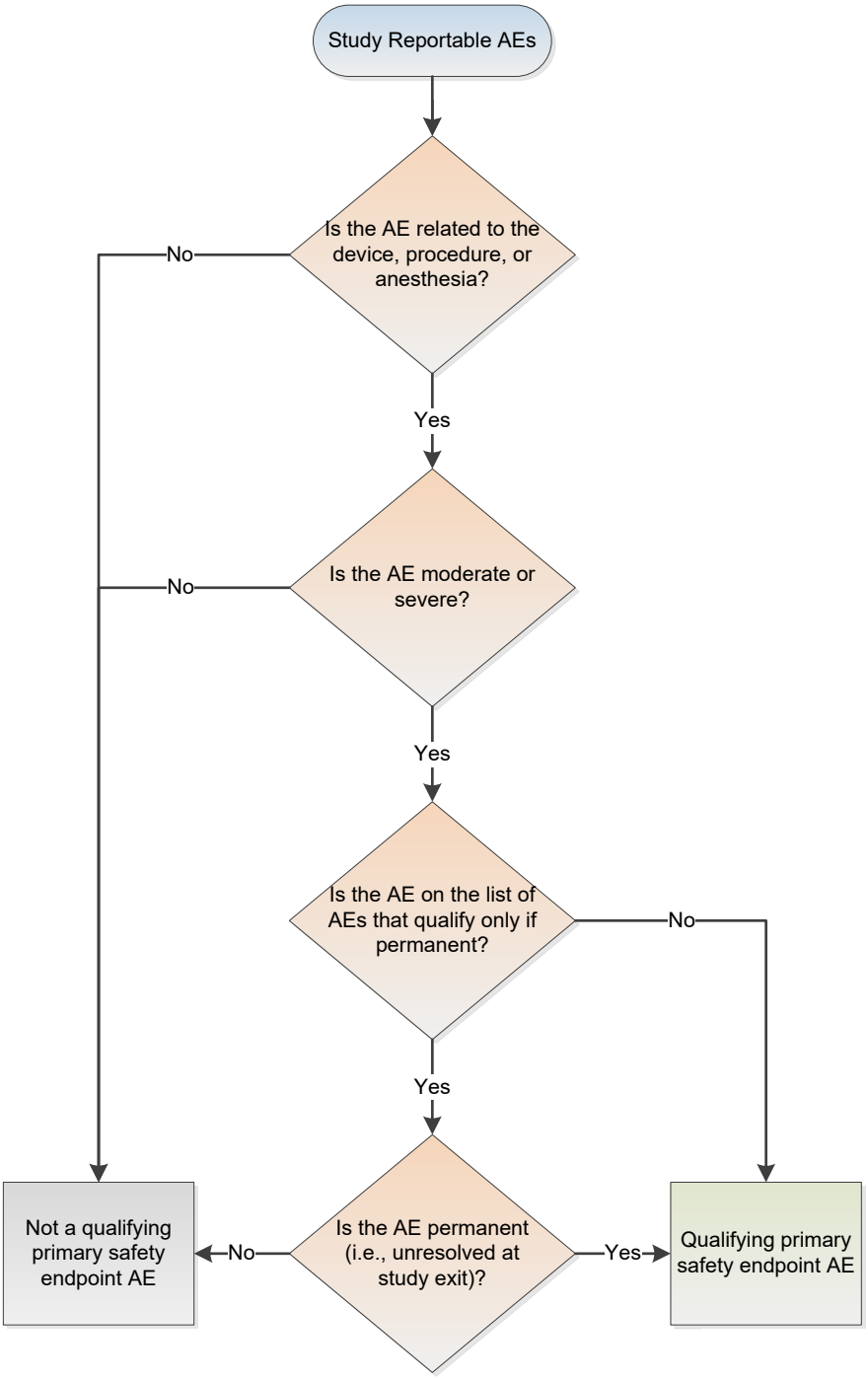


Figure 3: Qualifying Primary Safety Endpoint AE Flow Chart