Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE)

NCT02844465
Study Protocol
09 APRIL 2018

Medtronic

Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE)

Clinical Investigational Plan

Version 4.0

09 APRIL 2018

CIP Number: CS-05000

IDE Number: G150255

Study Sponsor:

Medtronic Navigation, Inc.

Clinical Investigational Plan Signature Page

The SLATE study is a prospective, single-arm, multicenter study. The study is being conducted to evaluate the safety and efficacy of the Visualase® MRI-Guided Laser Ablation System.

I/we acknowledge that I/we have read, understood and agree to abide by all conditions, instructions and restrictions contained in the above mentioned Clinical Investigational Plan. I/we agree to carry out all of its items in accordance with applicable regulations, and in full compliance with the guidelines.

Investigational Site Name		
First and Last Name	**Signature**	**Date (dd/MMM/yyyy)**

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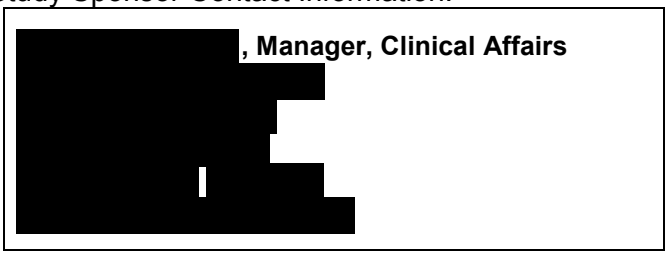
I. SPONSOR CONTACT INFORMATION

Medtronic contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the sites as needed and to the FDA with annual reports; however, personnel changes do not necessitate a protocol amendment.

Study Sponsor Contact Information:



Monitoring Contact Information:

II. NATIONAL PRINCIPAL INVESTIGATORS

Table 1: National Principal Investigators' Contact Information

Committee Member	Contact information
[redacted]	[redacted]
[redacted]	[redacted]

1 SYNOPSIS

Title

Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE)
Protocol Number: CS-05000
IDE Number: G150255

Purpose

The purpose of this study is to evaluate the safety and efficacy of the Visualase® MRI-Guided Laser Ablation System (Visualase System).

Design

Prospective, single-arm, multicenter study

Medical Device

The Visualase System comprises four components: a laser energy source, a cooled laser applicator, a circulating pump for circulating coolant through the applicator, and a computer workstation with magnetic resonance imaging (MRI) analysis software for determination and visualization of relative changes in tissue temperature during surgical ablation.

All devices used in this study are FDA cleared and commercially released. Devices become investigational only when accessed or opened with the intent to be used within the context of the study.

Objective and Endpoints

Objective: 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)

Primary Safety Endpoint
Incidence of qualifying device-, procedure-, or anesthesia-related adverse events (AEs) (defined in Appendix F) through 12 months following the Visualase procedure

Primary Efficacy Endpoint
Seizure freedom (defined as Engel Class I, Appendix C) at 12 months following the Visualase procedure

Secondary Endpoints

1. Seizure freedom (defined as Engel Class I, Appendix C) at 12 months following the Visualase procedure compared to historical control for continued medical therapy
2. Seizure freedom (defined as Engel Class I, Appendix C) 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 C) at 12 months following the Visualase procedure compared to historical control for open surgical resection

Subject Population

The study subject population is adult patients with medically intractable (per the definition by the International League Against Epilepsy[1]) mesial temporal lobe epilepsy

(MTLE), with radiological and electrophysiological evidence consistent with unilateral focal seizure onsets.

A minimum of 150 subjects will undergo the Visualase procedure and be evaluated at up to 25 sites in the United States. To account for attrition, up to 215 subjects may be enrolled.

The duration of subject participation from enrollment through study exit is expected to be approximately 13 months.

Treatment

Following informed consent, 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.

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. Refer to Table 2 for required study visits and required assessments/procedures during each visit.

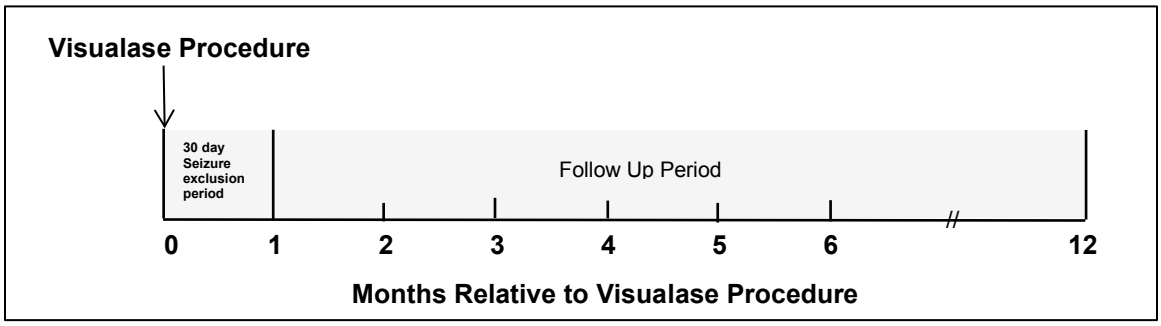


Figure 1: Study Design

Inclusion Criteria

1. Adult subjects ≥ 18 years of age and ≤ 70 years of age at the time of enrollment
2. History of medically refractory (or intractable) MTLE, defined per the International League Against Epilepsy (ILAE)[1] as: failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom, as determined by the Investigator
3. If the subject has a vagus nerve stimulator (VNS), the subject must have failed to achieve sustained seizure freedom with the VNS implanted for at least 6 months prior to enrollment
4. On stable antiepileptic drugs (AEDs) (and/or stable VNS setting, if applicable) for 30 days prior to the procedure and compliant with medication use, as reported by the subject

5. An average of at least 1 complex partial or secondarily generalized seizure compatible with MTLE per month, for a minimum of the last 12 months prior to enrollment (i.e., at least 12 qualifying seizures in the 12 months prior to enrollment)
6. Subject's seizure symptoms and/or auras are compatible with MTLE
7. Based on video EEG obtained within 24 months of enrollment, evidence of seizures from one temporal lobe consistent with MTLE. If the video EEG was obtained more than 12 months prior to enrollment, an interictal EEG done within 12 months of enrollment must show interictal spikes in the same distribution as seen in the previous video EEG monitoring.
8. Based on MRI obtained within 24 months prior to enrollment, evidence consistent with mesial temporal lobe sclerosis (defined as: mesial temporal atrophy accompanied by either increased signal on T2-weighted image, indicative of gliosis, or accompanied by loss of internal architecture in the hippocampus). If there is evidence of a change in clinical seizure symptoms/severity or of a brain injury since the MRI, a repeat MRI must be obtained to confirm eligibility.
9. Subject is willing and able to remain on stable AEDs (and stable VNS setting, if applicable), as directed by their treating physician, for 12 months following the Visualase procedure
10. Subject is able to complete study assessments in English or Spanish language
11. According to Investigator judgment, subject is willing and able to comply with protocol requirements (e.g., follow-up visit schedule, evaluations, compliance with AED regimen)

Exclusion Criteria

1. Subject is unwilling or unable to sign the study informed consent form (ICF)
2. Subject is pregnant prior to the Visualase procedure or intends to become pregnant during the course of the study
3. Subject is currently implanted with a device contraindicating MRI, including deep brain stimulation or responsive neurostimulator
4. Subject has progressive brain lesions and/or tumors not associated with epileptic disease state
5. Subject has a history of previous intracranial surgery for treatment of epileptic seizures, including intracranial resections, stereotactic radiosurgery, or deep brain stimulation
6. Subject has persistent (based on medical judgment) extra-temporal or predominant contralateral focal interictal spikes or slowing, or generalized interictal spikes on EEG
7. Subject has seizures with contralateral or extra-temporal ictal onset on EEG
8. Subject's aura and/or ictal behavior suggest an extra-temporal focus

9. Subject has evidence on MRI of epileptogenic extra-temporal lesions, dual pathology within the temporal lobe, or contralateral hippocampal increased T2 signal changes and/or loss of internal architecture
10. If additional testing (e.g., PET, SPECT, invasive EEG or MEG) has been performed, results are discordant with the seizure focus scheduled for ablation
11. As reported by the subject or in the opinion of the Investigator, the subject is not compliant with AED medication requirements
12. Subject has an IQ < 70, based on the Wechsler Abbreviated Scale of Intelligence (WASI or WASI-II) or Wechsler Adult Intelligence Scale Full Scale IQ or General Ability Index (WAIS-III or WAIS-IV FSIQ or GAI) performed within 12 months prior to enrollment, or after enrollment but prior to the procedure
13. Subject has been diagnosed with dementia or other progressive neurological disease
14. Subject has an unstable major psychiatric illness, psychogenic non-epileptic seizures, or medical illness that would contraindicate the Visualase procedure or affect the neuropsychological assessments
15. Subject is currently participating in other research that may potentially interfere with SLATE endpoint(s), as determined by the Investigator or Sponsor
16. Subject is allergic to gadolinium

Clinical Procedures

Subjects will be considered enrolled upon signing and dating the ICF and will be exited from the study upon completion of Follow-up Visit 4 twelve months following the Visualase procedure, or upon withdrawal. Required study visits and procedures are outlined in the Schedule of Events (Table 2) below.

Table 2. Schedule of Events

Assessment/Procedure	Enrollment / Screening	Baseline	Visualase Procedure	Follow-up Visit 1 14 days (±7days)	Follow-up Visit 2 3 mos (90±14 days)	Follow-up Visit 3 6 mos (180±30 days)	Follow-up Visit 4 12 mos (365+45 days)	Unscheduled Visit
Informed consent	X							
Demographics	X							
Medical/surgical history (including MRI & video EEG)	X[1]							
Epilepsy/seizure history	X							
AED & psychotropic medications recorded[2]	X	X	X	X	X	X	X	X[3]
Pregnancy test	X		X[4]					
IQ test[5]	X[6]							
Neurological exam, including oculomotor nerves & confrontation visual field test for AE reporting		X		X	X	X	X	
Adverse event assessment	X	X	X	X	X	X	X	X
Healthcare services utilization assessment			X	X	X	X	X	X
Boston Naming Test		X[6]				X	X	
COWA (FAS)		X[6]				X	X	
Emory Semantic Fluency Tasks		X[6]				X	X	
Emory Famous Faces Naming/Recognition		X[6]				X	X	
Rey Auditory Verbal Learning Test		X[6,7]				X[8]	X[7]	
WMS-IV Visual Reproduction Test		X[6]				X	X	
WMS-IV Verbal Paired Associates		X[6]					X	
Beck Depression Inventory-II[9]		X				X	X	
Beck Anxiety Inventory[9]		X				X	X	
QOLIE-31[9]		X				X	X	
SF-36[9]		X				X	X	
Seizure Severity Questionnaire Version 3[9]		X				X[10]	X[10]	
Seizure diary review[11]	X	X[3]	X[3]	X	X	X	X	X[3]
Seizure classification[13]	X	X[3]	X[3]	X	X	X	X	X[3]
Research MRI		X				X		
Visualase procedure (including pre & post ablation MRI scans)			X					
Pain NRS			X[12]					
Assessment of driving and employment/school status		X					X	
Neuro-ophthalmologic exam of acuity, fields and extraocular movements[14]		X[6]			X	X[15]	X[15]	X[16]

AED=Antiepileptic drugs; COWA (FAS)=Controlled Oral Word Association Test; EEG= electroencephalogram; QOLIE-31=Quality of Life in Epilepsy Inventory; WAIS=Wechsler Adult Intelligence Scale; WASI=Wechsler Abbreviated Scale of Intelligence; WMS-IV=Wechsler Memory Scale

[1]Includes past AEDs, MRI, and video EEG (and Wada test, functional MRI, MEG, PET and/or SPECT scan if available)
[2]AEDs and their dosages should remain stable from 30 days prior to the procedure through the 12 month post procedure visit.
[3]Assessments should be done if possible.
[4]To be performed within 7 days prior to the Visualase procedure for all females of childbearing potential
[5]WAIS-III or WAIS-IV (FSIQ or GAI), or WASI or WASI-II are acceptable for screening. If scores are not available in the medical record, one of these assessments will be administered post-consent.
[6]Results of assessments performed within 12 months prior to enrollment may be used.
[7]Administer Form A.
[8]Administer Form GE-AB.
[9]Self-reported by subjects.
[10]The Seizure Severity Questionnaire is completed only by subjects who have had seizures within the 4 weeks preceding the 6- and/or 12-month visits.
[11].The seizure diary will be provided to the subject after consent, prior to submission to the Pre-Surgical Evaluation Committee. Subsequent reviews shall occur at indicated timepoints. Reviews at the Baseline Visit, Visualase Procedure and Unscheduled Visits are encouraged, though not required.
[12]The pain scale is to be completed following the Visualase procedure but prior to discharge.
[13]Seizure classification will initially be conducted after consent, prior to submission to the Pre-Surgical Evaluation Committee, and then amended throughout the subject's participation in the study if new seizure types occur.
[14]Subjects who were enrolled and received treatment under a CIP version prior to 4.0 should be reconsented to have a neuro-ophthalmologic exam at their next scheduled study visit.
[15]Any subject consenting to CIP 4.0 who has an abnormal neuro-ophthalmologic finding at any follow-up visit is required to have neuro-ophthalmologic exams at subsequent study follow-up visits until the finding is resolved or until Follow-up Visit 4, whichever occurs first.
[16]If a subject consented to CIP 4.0 has symptoms of a potential vision-related adverse event prior to the 3-month follow-up visit, a neuro-ophthalmologic exam will be performed for evaluation.

2 INTRODUCTION

2.1 Study Purpose

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) (defined in Appendix F) through 12 months following the Visualase procedure. To assess efficacy, the primary endpoint will evaluate seizure freedom (defined as Engel Class I, Appendix C) at 12 months following the Visualase procedure.

The cleared indication for use of the prescription-only Visualase System is "to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under magnetic resonance imaging (MRI) guidance" for a number of surgery types, including neurosurgery. Based on the results of this study, the Sponsor is seeking expanded indications for use of the Visualase System for temporal lobe epilepsy.

2.2 Study Description

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. To account for attrition, up to 215 subjects may be enrolled. Enrollment rates across sites will be

monitored, but there is not a minimum or maximum requirement for the number of subjects enrolled at each site.

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. Accordingly, the expected total study duration is approximately 65 months, representing approximately 52 months of enrollment and approximately 13 months of subject participation.

3 BACKGROUND AND JUSTIFICATION

3.1 Background

Epilepsy is a chronic neurological condition characterized by recurrent seizures. Approximately 3 million people in the United States have epilepsy,[2] and it is estimated that at least one-third of them become medically intractable, continuing to have seizures regardless of the number or type of anti-epileptic drugs (AEDs) used.[3] About 150,000 new cases of epilepsy will be diagnosed in the United States each year.[4] Uncontrolled seizures lead to a wide variety of medical consequences (e.g., trauma due to seizures, sudden death, depression, intermittent psychotic disorders) and significant lifestyle limitations and social handicaps (e.g., loss of driving privileges, difficulty getting and maintaining a job). Epilepsy results in an estimated annual cost of $15.5 billion in medical costs and lost or reduced earnings and production.[5]

Perhaps the most common type of epilepsy in adults is temporal lobe epilepsy (TLE), which has been reported to represent about 9% of the entire population of patients with epilepsy[6;7] and as much as 66% of all patients with localized-epilepsy seen at tertiary referral centers.[8] Epilepsy surgery has gained an important role in the treatment of medically intractable epilepsy, especially TLE, over the past few decades because of the development of better seizure localization techniques, safer surgical techniques, and better surgical tools.

Two surgical resection techniques have been commonly utilized to treat mesial temporal epilepsy, namely anterior temporal lobectomy with mesial temporal resection (ATL) and selective amygdalohippocampectomy (SAH). Schramm reviewed 53 studies in which various temporal lobe resections were performed for medically intractable mesial temporal lobe epilepsies and found consistently high rates of seizure freedom at one-year post-operative follow-up.[9] In the most referenced randomized TLE study by Wiebe et al, seizure freedom occurred in 58% of the group assigned to surgery versus 8% for the patients who continued with medical therapy only.[10] A second randomized trial provided confirmation of these results; 73% of mesial TLE patients who underwent temporal lobe resection were seizure-free after 2 years compared to 0 patients with medical treatment.[11] Despite these, and many other well-documented high rates of seizure-freedom following surgical resection of temporal foci, the utilization of temporal lobectomy has not increased from 1990 to 2008[12] but has decreased, according to a recent survey.[13] Not only has surgery for epilepsy remained arguably the most underused of all proven effective therapies, even those patients who are referred for surgery wait for an average of 22 years after onset of epilepsy for that referral,[14] often too late to prevent or reverse the disabling adverse medical, psychological and social consequences of recurrent seizures. Factors like prolonged recovery, surgical invasiveness, and potential morbidities such as neurological deficits have been obstacles for completion of more epilepsy surgeries.

3.2 Clinical Rationale for the Study Design

There is growing interest from surgeons and growing demand from patients for minimally invasive techniques to address intractable epileptogenic foci. Vagus nerve stimulation and the FDA-approved responsive neurostimulation therapy[15] have each been shown to reduce the number of seizures a patient suffers but rarely attain the goal of seizure freedom demonstrated with surgical resection. Surgeons have used several minimally- or non-invasive surgical tools and techniques including stereotactic radiosurgery (SRS)[16] and stereotactic radiofrequency (SRF) ablation[17] to successfully target and destroy the epileptogenic targets that are otherwise resected during craniotomy, showing promise in producing rates of seizure freedom similar to open surgical resection. For example, Liscak et al noted a 78% seizure-freedom rate at 2 years using radiofrequency,[17] while Barbaro et al demonstrated 67% seizure freedom at three years using Gamma Knife® radiosurgery (GKRS), which has a delayed-onset of the treatment effect.[18] Although these methods show promise, there are morbidities associated with the procedures. Quigg et al provided a review of minimally invasive techniques for epilepsy and discussed the shortcomings of SRS and SRF. The primary shortcoming of SRS is the delay in therapeutic effect. Maximal seizure decrease doesn't occur until 12-18 months after surgery, potentially leading patients to seek additional therapy in the interim. Additionally, although infrequent, the possibility of tumor generation attributed to the therapy has occurred. For SRF, the created lesion size is often insufficient to interrupt the epileptic circuit, leading to poor seizure outcomes.[19]

The Visualase System is a minimally invasive tool that has also been used to destroy epileptogenic targets. The advantage of the Visualase procedure is three-fold: 1) it is a minimally-invasive procedure, 2) effects are on par with other minimally invasive surgeries, and 3) the procedure allows for further intervention if required. The Visualase System has been on the market for 8 years, with a low rate of complications. Published case series and case reports of a total 37 patients revealed 2 homonymous hemianopias (5.4%), 2 hemorrhages (5.4%, one of which was asymptomatic and did not require intervention), 1 transient memory impairment, and 1 transient leg weakness.[20-26] In a recent case series, seizure-freedom rate in a comparable population was reported as 54%.[23;26] Collective work from several single-center experiences presented as abstracts reported that 48-50% of patients who underwent the Visualase System ablation procedure achieved seizure freedom (Engel Class I) through twelve months. Perhaps the more distinguishing feature of the Visualase System is the lack of cognitive deficit compared to resection.[27;28] In a recently published study, patients with TLE undergoing either resection or laser ablation using Visualase were given a series of cognitive tests. No patient who underwent the laser ablation procedure had cognitive decline, compared to 82% of resection patients who had declines on one or more measures.[29]

To build upon these early positive results, a prospective, single-arm, multicenter study has been designed to demonstrate the safety and efficacy of the Visualase System in subjects with MTLE.

Attiah et al 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 in order to provide quality of life (QOL) improvements equivalent to anterior temporal lobectomy (ATL).[30] The meta-analysis included records of over 25,000 cases of ATL and the available dataset for laser ablation from a recent multi-center study. The results of the analysis revealed that achieving 43% Engel I outcomes and no more than 40% late mortality/morbidity with laser ablation is needed in order to be grossly equivalent to ATL. Although constrained by certain analytic factors and limited to the

available data for laser ablation, this analysis provides the best current estimate for a success or performance threshold of laser ablation to match the well-documented long-term effectiveness of ATL. Therefore, this study compares safety and efficacy outcomes of laser ablation to the threshold determined by Attiah et al.[30]

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.

3.3 Justification for Human Use

The Visualase System has been cleared by the FDA for human use in the United States since 2007. Peer-reviewed publications describe patients achieving seizure reduction or freedom with few adverse events. However, no controlled clinical trials for MTLE have been undertaken to investigate safety and efficacy of the device in this population.

4 SYSTEM DESCRIPTION AND INTENDED USE

The Visualase System (Figure 2 and 3) is 510(k) cleared and indicated for use to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under MRI guidance in medicine and surgery in cardiovascular thoracic surgery (excluding the heart and the vessels in the pericardial sac), dermatology, ear-nose-throat surgery, neurosurgery, plastic surgery, orthopedics, pulmonology, radiology, and urology, for wavelengths 800nm through 1064nm.

The Visualase System comprises four components: a cooled laser applicator, a pump for circulating coolant through the applicator, a laser energy source, and a computer workstation with MRI analysis software for determination and visualization of relative changes in tissue temperature during surgical ablation. A software application running on the workstation allows the workstation user to control the laser output and to operate the coolant pump from the workstation interface.

Figure 2: Visualase Thermal Therapy System

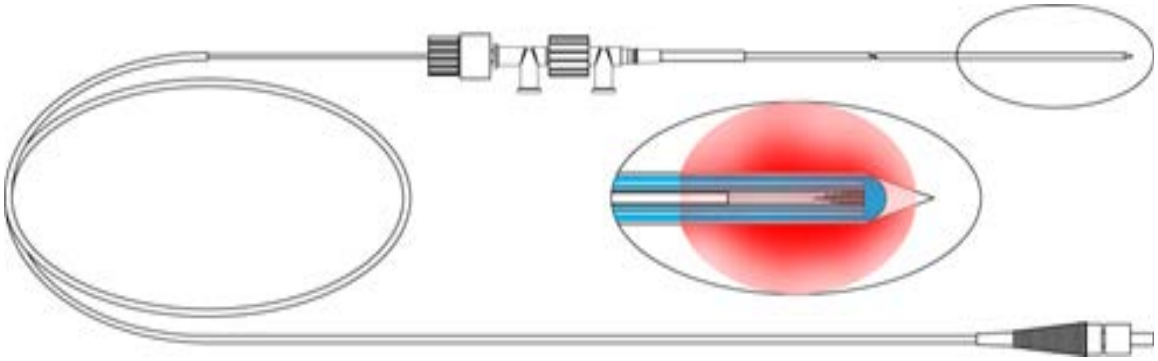


Figure 3: Visualase Cooled-Laser Applicator System (VCLAS)

The Visualase Cooled Laser Applicator System (VCLAS) consists of a Laser Diffusing Fiber (LDF) and a Cooling Catheter System (CCS), which provides cooling for the tissue and LDF in contact with the CCS. The Envision workstation and software transports and processes the images and displays the images on the workstation to provide visualization and facilitate manipulation of the data extracted by the image-processing tools. An example of the images and information that is displayed to aid the surgeon during the procedure is shown in Figure 4 and 5 below.

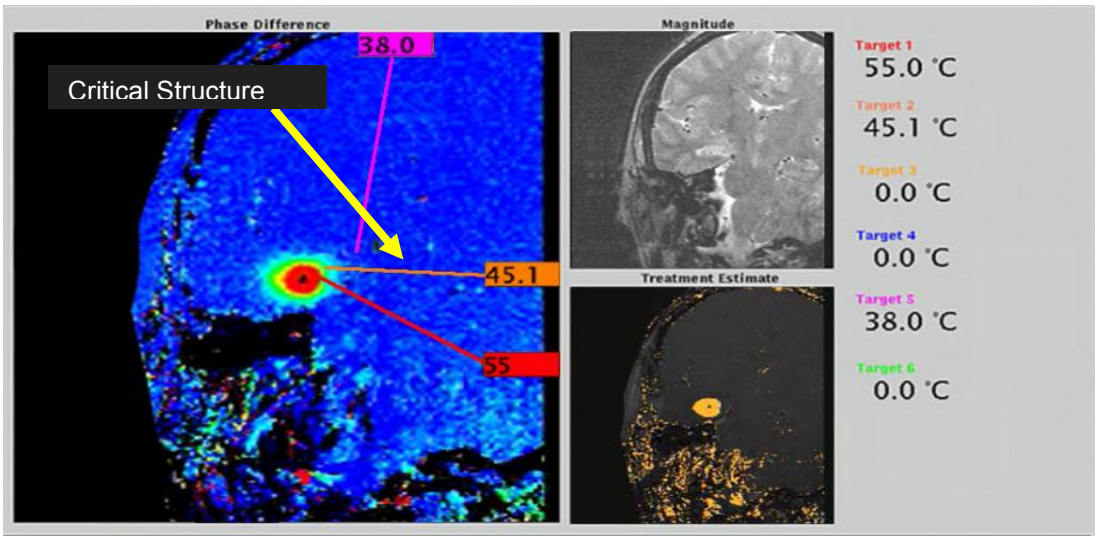


Figure 4: Temperature limits are set to protect critical structures

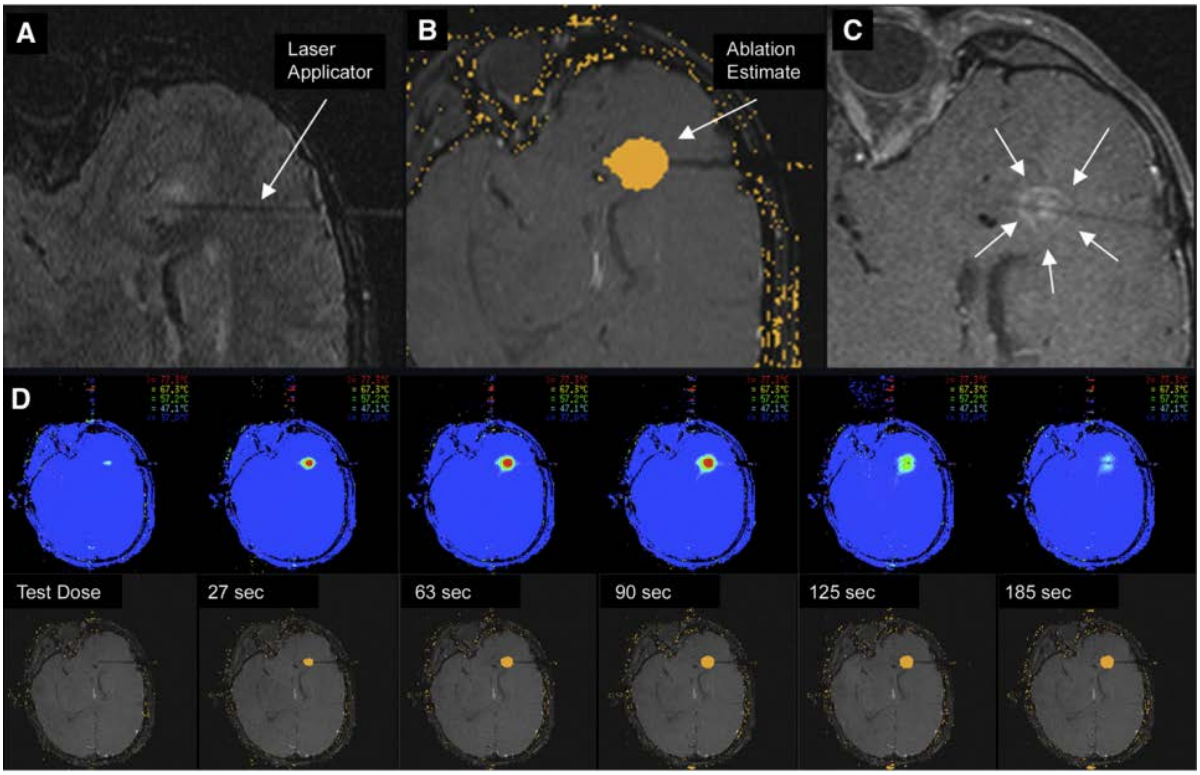


Figure 5: Visualase System software images and near real-time temperature information.

Thermal ablation of cingulated gyrus tuber: A) Pre-therapy MRI confirming placement of laser applicator into target tuber. B) Software estimate of thermal damage created after 90-second duration of 980nm laser at 11.25 W. C) Immediate post-ablation contrast-enhanced T1 MRI image with enhanced border defining extent of thermal ablation. D) Representative thermal images and damage estimates selected from over 40 images acquired during the ablation cycle. Images demonstrate heating up to 90s followed by immediate cooling after termination of laser delivery. Images courtesy of [redacted]

Principles of Operation

The Visualase System utilizes the properties of light at a specified wavelength (i.e., 980nm, but in a range that includes 800nm to 1064nm) to direct photon energy to brain tissue in a form that is absorbed by the surrounding cells, causing elevation of tissue temperature and controlled tissue damage through coagulative necrosis. For temperatures greater than 60ºC, cell death is instantaneous. For temperatures between 44 and 59ºC, cell death is time dependent. Typically during the Visualase procedure, the tissue temperature is held to below 90ºC to avoid tissue vaporization.[31-40]

The coagulation/necrosis procedure is frequently monitored by converting changes in MRI images to real-time thermal maps and estimating thermal damage using an Arrhenius-based damage model, both of which are displayed on the workstation. This information helps the surgeon monitor and control the area that is receiving the photon energy and being ablated.

In typical use, as per its labeling, the surgeon places the Visualase laser applicator, usually employing stereotactic techniques (using either frame-based or frameless system), into the specified target in the brain. The applicator is MRI-compatible and the coagulation/necrosis can be performed inside the MRI magnet (Figure 6). After securing the applicator, the patient is transferred to the MRI scanner, where s/he undergoes imaging to confirm the correct position of the laser applicator. Safety markers can be placed on the MRI images, which can be set by the surgeon to specify key structures in the brain that trigger the laser to be turned “off” upon reaching user-defined temperature thresholds. During the coagulation/necrosis procedure, the Visualase System processes images using proton resonance-frequency (PRF) shift analysis and image subtraction to relate the changes in the complex phase angle compared to the relative changes in tissue temperature. Thus, the laser thermal therapy procedure is performed under MR-image guidance. The image data may be viewed in a number of different formats, and the values of data at certain selected points in the brain may be monitored and/or displayed over the time of treatment. After these images are acquired and a satisfactory necrosis/coagulation has been performed according to the surgeon, then typically a post-contrast enhanced T1-weighted image is acquired to define the boundary of thermal damage in the brain.

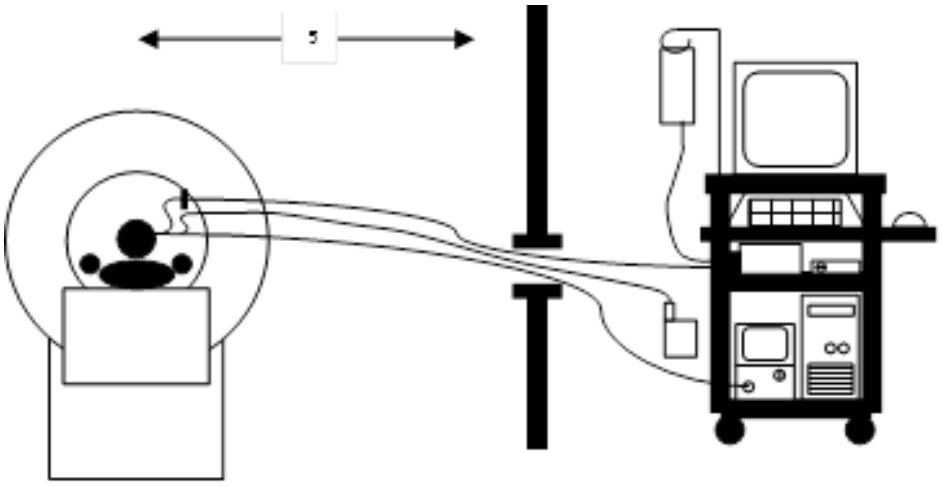


Figure 6: Visualase System set up when in use with MRI

Tools & Procedures Used in Conjunction with the Visualase System

Typical stereotactic and navigation modalities employed in general surgery and neurosurgery techniques may be used in conjunction with the Visualase System. Frame-based stereotactic techniques as well as use of navigation technologies are common in neurosurgical procedures. Open resections and craniotomies also use such procedural and targeting methods to a certain extent. The Visualase System is a standalone tool/device and does not require integration nor are there compatibility or restriction concerns with current stereotactic frames and navigation systems.

The study will be conducted using the components described in Table 3 below. The instructions for use of the devices used in this study are provided in their respective manuals. Future releases of products will be included in the study upon FDA clearance.

Table 3: System Component Information

Medtronic Part Number	Component Description
[redacted]	Sterile, single use, patient contacting, Visualase Cooled Laser Applicator System with 0.4mm core fiber, 3mm tip
[redacted]	Sterile, single use, patient contacting, Visualase Cooled Laser Applicator System with 0.4mm core fiber, 10mm tip
[redacted]	Sterile, single use, patient contacting, Visualase Cooled Laser Applicator System with 0.6mm core fiber, 15mm tip
[redacted]	Visualase Thermal Therapy System (capital system)
None (Component of [redacted])	[redacted] Laser System
None (Component of [redacted])	[redacted]

The following optional accessory may also be used during the Visualase procedure.

Medtronic Part Number	Component Description
[redacted]	Visualase Neuro Accessory Kit – includes: (1) titanium bone anchor, (1) plastic bone anchor, and (1) stiffening stylet
[redacted]	Visualization stylet (1)

5 REGULATORY COMPLIANCE

The study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with 21 CFR Parts 11, 50, 54, 56 and 812. The study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent Institutional Review Board (IRB) before initiating a study, continuing review of an ongoing study by an IRB, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The study will be conducted in accordance with the principles that have their origin in the Declaration of Helsinki. The principles of the Declaration of Helsinki have been implemented through the patient informed consent process, IRB approval, study training,

clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

Approval of the Clinical Investigational Plan (CIP) is required from the following entities prior to any study procedures at a study site:

- Medtronic
- FDA
- Site IRB

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above-mentioned entities prior to implementation of the revised CIP at that site.

Each site's IRB will also be required to approve any subject recruitment materials.

Any additional requirements imposed by the site's IRB shall be followed.

6 METHODS

6.1 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 mesial temporal lobe epilepsy (MTLE).

6.2 Study Endpoints

The following endpoints will be used to evaluate the study objective.

6.2.1 Primary Safety Endpoint

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

6.2.2 Primary Efficacy Endpoint

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

6.2.3 Secondary Endpoints

1. Seizure freedom (defined as Engel Class I, Appendix C) at 12 months following the Visualase procedure compared to historical control for continued medical therapy
2. Seizure freedom (defined as Engel Class I, Appendix C) 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 C) at 12 months following the Visualase procedure compared to historical control for open surgical resection

6.2.4 [redacted]

12. [redacted]

6.3 Subject Selection Criteria

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria. IRB approval of the SLATE CIP and informed consent form must be obtained prior to enrolling patients in the study.

Enrollment of the subject must occur prior to any study specific procedures.

6.3.1 Inclusion Criteria

1. Adult subjects ≥ 18 years of age and ≤ 70 years of age at the time of enrollment
2. History of medically refractory (or intractable) MTLE, defined per the International League Against Epilepsy (ILAE)[1] as: failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom, as determined by the Investigator
3. If the subject has a vagus nerve stimulator (VNS), the subject must have failed to achieve sustained seizure freedom with the VNS implanted for at least 6 months prior to enrollment
4. On stable antiepileptic drugs (AEDs) (and/or stable VNS setting, if applicable) for 30 days prior to the Visualase procedure and compliant with medication use, as reported by the subject
5. An average of at least 1 complex partial or secondarily generalized seizure compatible with MTLE per month, for a minimum of the last 12 months prior to enrollment (i.e., at least 12 qualifying seizures in the 12 months prior to enrollment)
6. Subject's seizure symptoms and/or auras are compatible with MTLE
7. Based on video EEG obtained within 24 months of enrollment, evidence of seizures from one temporal lobe consistent with MTLE. If the video EEG was obtained more than 12 months prior to enrollment, an interictal EEG done within 12 months of enrollment must show interictal spikes in the same distribution as seen in the previous video EEG monitoring.
8. Based on MRI obtained within 24 months prior to enrollment, evidence consistent with mesial temporal lobe sclerosis (defined as: mesial temporal atrophy accompanied by either increased signal on T2-weighted image, indicative of gliosis or by loss of internal architecture in the hippocampus). If there is evidence of a change in clinical seizure symptoms/severity or of a brain injury since the MRI, a repeat MRI must be obtained to confirm eligibility.
9. Subject is willing and able to remain on stable AEDs (and stable VNS setting, if applicable), as directed by their treating physician, for 12 months following the Visualase procedure
10. Subject is able to complete study assessments in English or Spanish language.
11. According to Investigator judgment, subject is willing and able to comply with protocol requirements (e.g., follow-up visit schedule, evaluations, compliance with AED regimen)

6.3.2 Exclusion Criteria

1. Subject is unwilling or unable to sign the study informed consent form (ICF)
2. Subject is pregnant prior to the Visualase procedure or intends to become pregnant during the course of the study
3. Subject is currently implanted with a device contraindicating MRI, including deep brain stimulation or responsive neurostimulator
4. Subject has progressive brain lesions and/or tumors not associated with epileptic disease state
5. Subject has a history of previous intracranial surgery for treatment of epileptic seizures, including intracranial resections, stereotactic radiosurgery, or deep brain stimulation
6. Subject has persistent (based on medical judgment) extra-temporal or predominant contralateral focal interictal spikes or slowing, or generalized interictal spikes on EEG
7. Subject has seizures with contralateral or extra-temporal ictal onset on EEG
8. Subject's aura and/or ictal behavior suggest an extratemporal focus
9. Subject has evidence on MRI of epileptogenic extra-temporal lesions, dual pathology within the temporal lobe, or contralateral hippocampal increased T2 signal changes and/or loss of internal architecture
10. If additional testing (e.g., PET, SPECT, invasive EEG or MEG) has been performed, results are discordant from the seizure focus scheduled for ablation
11. As reported by the subject or in the opinion of the Investigator, subject is not compliant with AED medication requirements
12. Subject has an IQ < 70, based on the Wechsler Abbreviated Scale of Intelligence (WASI or WASI-II) or Wechsler Adult Intelligence Scale Full Scale IQ or General Ability Index (WAIS-III or WAIS-IV FSIQ or GAI) performed within 12 months prior to enrollment, or after enrollment but prior to the procedure
13. Subject has been diagnosed with dementia or other progressive neurological disease
14. Subject has an unstable major psychiatric illness, psychogenic non-epileptic seizures, or medical illness that would contraindicate the Visualase procedure or affect the neuropsychological assessments
15. Subject is currently participating in other research that may potentially interfere with SLATE endpoint(s), as determined by the Investigator or Sponsor
16. Subject is allergic to gadolinium

6.4 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

1. Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.

2. A central review of subjects' epilepsy history, MRI and EEG will be performed to confirm study qualification for the Visualase procedure.
3. Subject demographics will be collected pre-procedure in order to later assess possible characteristics that may influence endpoints.
4. Subjects will serve as their own controls for selected secondary endpoints.
5. A statistical analysis plan, which will document all pre-specified analyses and analysis methods, will be developed prior to analyzing data.
6. A modified intent-to-treat analysis will be performed on the study endpoints.
7. All study sites will use the same version of the Clinical Investigational Plan and Case Report Forms (CRFs).
8. All study personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials.
9. All study personnel will be trained on and required to follow the Clinical Investigational Plan.
10. An independent Data Monitoring Committee (DMC) will be used to safeguard the interests of study subjects, and to act as an advisory panel ensuring continued scientific validity and necessity. (See Appendix D.)
11. All study investigators will be required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators.
12. All neuropsychological assessments will be scored at a core laboratory.
13. Volumetric analysis of tissue ablation will be conducted at a core laboratory.

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

7 STUDY PROCEDURES

7.1 Investigator / Investigational Site Selection

All clinical investigators managing the subject's epilepsy must be qualified practitioners and experienced in the diagnosis and treatment of persons with epilepsy. All personnel administering neuropsychological assessments must be trained on assessment administration and/or licensed in psychometry.

The role of the Principal Investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and protection of the rights, safety and well-being of the subjects involved in the clinical investigation.

The Principal Investigator must:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results

The Principal Investigator must be able to demonstrate that the proposed investigational site:

- Has a sufficient number of eligible subjects needed within the recruitment period
- Has one or more qualified investigators, a qualified investigational site team and adequate facilities for the foreseen duration of the clinical investigation

Neurosurgeons performing cases as study investigators must have prior experience with the study procedure. Specifically, surgeons must demonstrate experience targeting the hippocampus in a stereotactic surgical procedure and must have hands-on experience using the Visualase system. This experience can be evidenced by any of the following, as attested to by the participating surgeon in writing:

1. At least 10 completed cases using the Visualase system for any target, including at least 5 cases for MTLE; or
2. At least 5 completed cases using the Visualase system for any target, and substantial experience (5 years or more) targeting the hippocampus in other stereotactic procedures (e.g., electrode placement); or
3. Surgeon has previously completed at least 3 cases using the Visualase system for any target. Surgeon may perform ongoing study cases only under direct supervision from a surgeon who meets criteria 1 and/or 2 above, until he/she has completed 10 cases under supervision.

Additionally, qualification requirements include, but are not limited to sites having adequate facilities, infrastructure, training and experience to provide comprehensive treatment and care of patients with MTLE, and to conduct clinical research studies.

7.2 Site Training

Prior to enrolling and treating subjects, site personnel will be trained on the CIP, relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study. All training documentation will be maintained in the study files.

Appropriate study personnel from each site (e.g., psychometrists/neuropsychologists) will be trained on administering the neuropsychological assessments per protocol.

7.3 Site Activation

Prior to performing study-related activities, all local regulatory requirements must be fulfilled, including but not limited to the following:

- IRB approval of the current version of the CIP and ICF
- FDA approval of the Investigational Device Exemption (IDE) application
- Fully executed Clinical Trial Agreement
- Financial Disclosure by Investigators
- Current curriculum vitae of Investigators
- Documentation of delegated tasks for all participating site staff
- Documentation of study training for all participating site staff

Additional requirements imposed by the IRB and FDA must be followed, if appropriate.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to subject enrollment.

7.4 Equipment Requirements

The following equipment must be available at each site to support study activities.

7.4.1 Visualase System

The Visualase System capital equipment (computer workstation, laser energy source and coolant pump) must be installed and available.

7.4.2 Visualase Procedure MRI

An MRI scanner must be available to acquire procedural scan sequences.

7.4.3 Research MRI

A 3-Tesla MRI scanner must be available to acquire research MRI scans at baseline and 6 months following the Visualase procedure. To maintain imaging consistency, the same scanner must be used for both research scans for each subject.

7.4.4 Neuro-ophthalmologic Exam

The site must have access to a qualified specialist (for example, a neuro-ophthalmologist or board-certified ophthalmologist) to oversee examinations of best corrected visual acuity, visual fields, and extraocular movements. Access to visual field testing using automated perimetry is required.

7.5 Assessments

Enrolled subjects will be required to complete all assessments. However, subjects who are unable to complete study assessments in English, but are able to complete assessments available in Spanish, will be required to complete all assessments except for Seizure Severity Assessment (7.5.4) and Neuropsychological Assessments (7.5.6).

7.5.1 Seizure Classification and Diary

Each subject's seizure types will be documented on the Seizure Classification eCRF, according to clinical manifestation and the subject's own description. A study Investigator will then classify seizure types per the International League Against Epilepsy (ILAE) classification. Seizure classification will initially be conducted after consent, prior to submission to the Pre-Surgical Evaluation Committee for review, and then amended throughout the subject's participation in the study if new seizure types occur.

Subjects will be given paper-based seizure diaries to document occurrence of seizures after enrollment through study exit. The seizure diary will be initially provided to the subject after consent, prior to submission to the Pre-Surgical Evaluation Committee. Seizure types will be recorded for each subject in concordance with the initial Seizure Classification eCRF. Seizure diaries will be reviewed with the subjects and collected by the site at specified visits. The site will enter seizure information into the Seizure Diary Summary eCRF. Recorded data shall include qualifiers needed to determine Engel Classification per Appendix C (e.g., nocturnal seizures only or generalized convulsion with AED discontinuation). A new seizure diary may be issued to the subject at each visit if needed.

7.5.2 Mood Assessments

Mood will be assessed using the following:

- Beck Depression Inventory® II – a 21-item self-reported instrument for measuring the presence and severity of depression in adults and adolescents. Each of the 21 items requires the respondent to endorse one of 4 options, scored 0 to 3, with increasing scores reflecting greater severity of a given depressive symptom.

- Beck Anxiety Inventory® – a 21-item self-reported instrument for measuring the severity of anxiety in adults and adolescents. Each of the 21 items requires the respondent to endorse one of 4 options, scored 0 to 3, with increasing scores reflecting greater severity of a given anxiety symptom.

7.5.3 Quality of Life Assessments

Change in health-related quality of life (QOL) will be assessed using the following:

- Quality of Life in Epilepsy-31 (QOLIE-31) - a self-reported survey containing multi-item measures of quality of life, emotional well-being, role limitations, social support/isolation, energy/fatigue, worry about seizure, medication effects, health discouragement, work/driving/social function, attention/concentration, language, memory, physical function, pain, and health perceptions. Results of the QOLIE-31 measures may be obtained from the Quality of Life in Epilepsy-89 (QOLIE-89) survey.
- SF-36 Health Survey version 2 (SF-36) – a widely used measure of health-related quality of life. The SF-36 contains 36 items that are divided into 8 different categories designed to evaluate the multidimensional aspects of health including: physical functioning, role limitations caused by physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations caused by emotional problems, and mental health. The 8 subscales can be aggregated into 2 summary scores, physical component summary and mental component summary, with higher scores representing better health status.

7.5.4 Seizure Severity Assessment

Seizure severity will be assessed using the following:

- Seizure Severity Questionnaire (SSQ) Version 3 - a review of various aspects of seizures completed by the person who has seizures, possibly with help from people who have observed the seizures. There are 11 questions asking about events before, during, and after typical seizures. The SSQ is only required to be completed by subjects who have seizures within the 4 weeks preceding the 6-month and/or 12-month visits. Subjects who are seizure free following the Visualase procedure are not required to complete the SSQ.

7.5.5 Pain Assessment

Pain will be assessed using the following:

- Pain Numeric Rating Scale (Pain NRS) - a unidimensional measure of pain intensity in adults. The subject selects a whole number (0-10 integer) that best reflects the intensity of their pain. The NRS is anchored by terms describing pain severity extremes, where 0 represents no pain and 10 represents the worst pain possible.[41] The pain scale will be completed after the Visualase procedure but prior to discharge. If multiple pain scales are completed, the result of the last pain scale prior to discharge will be reported for the study.

7.5.6 Neuropsychological Assessments

A neuropsychology specific manual of operations will be provided to all sites. The purpose of the manual will be to clearly delineate specific test administration instructions to specific normative databases and to otherwise standardize all procedures and anticipated scenarios that might occur as part of the neuropsychological assessment.

Materials for administration of the neuropsychological assessments will be provided to sites.

- Boston Naming Test – a 60-item confrontation naming test to measure word retrieval performance. The subject is asked to name what they see in a picture book, and the time it takes for them to respond is recorded.
- Controlled Oral Word Association Test (COWA) (FAS) – a measure of verbal fluency. Subjects are given one minute to name as many words as possible beginning with the letter F. The procedure is then repeated for letters A and S.
- Emory Semantic Fluency Paradigm – a measure of semantic memory using everyday objects. Subjects are given a certain amount of time to name as many items in a category.
- Emory Famous Faces Naming/Recognition – a measure of semantic memory using proper nouns (famous faces). Subjects are shown photographs of famous people and are given 20 seconds to identify each image.
- Rey Auditory Verbal Learning Test – a test that evaluates verbal learning and memory (recall and recognition). Subjects are given a list of 15 unrelated words repeated over five different trials and asked to repeat. Another list of 15 unrelated words are given and repeated. The subject must then repeat the original list of words and then again after 30 minutes.
- Wechsler Memory Scale (WMS-IV) Visual Reproduction Test - a measure of visual memory. Subjects are shown an image for 10 seconds and then asked to draw the image.
- Wechsler Memory Scale (WMS-IV) Verbal Paired Associates - a measure of verbal memory for associated word pairs. The subject is read 10 or 14 word pairs. The subject is then read half the word pair and asked to respond with the corresponding other half of the pair.

7.6 Magnetic Resonance Imaging

A Research MRI manual of operations will be provided to all sites. The purpose of the manual will be to clearly delineate specific MR image sequences to be obtained as well as provide scanner specific parameters.

The following MRI scans are to be performed:

- Research scan at the Baseline visit and 6 months following the Visualase procedure. ***(Note: the subject must be scanned on the same scanner at the Baseline visit and at the 6-month visit.)***
    - Isotropic T1 MPRAGE, sagittal plane
    - Isotropic T2, sagittal plane
    - T2-TSE/TFE, coronal plane
    - Isotropic DTI, axial plane
- Procedural scans
    - Pre-ablation: volumetric T1 and/or T2 weighted sequences with multiplanar reformatting (MPR) to verify proper positioning through the

desired trajectory and to select appropriate imaging planes for monitoring during ablation

- Ablation: per institutional standard
- Post ablation: T1 with gadolinium contrast volumetric series in any plane to visualize the lesion with MPR aligned with or perpendicular to the laser fiber, and T2 FLAIR and DWI. Post ablation scans should be conducted immediately following the procedure. If this is not feasible (e.g., the subject required pre-ablation gadolinium for trajectory planning and another dose cannot be administered), the post-ablation scans may be completed prior to discharge.

7.7 Neuro-ophthalmologic Exam

A neuro-ophthalmologic exam manual will be provided to sites to delineate specific procedures for exams of best-corrected acuity, visual fields, and extraocular movements, performed under the guidance of a qualified specialist (for example, a neuro-ophthalmologist or board-certified ophthalmologist). Visual field testing using automated perimetry is required.

7.8 Data Collection

Data will be collected using an electronic data capture system. CRF Instructions will include details regarding appropriately completing eCRFs and allowable data on eCRFs. Data collection requirements at each visit are summarized in Table 4 below.

Table 4: Data Collected at Subject Visits

Case Report Forms	Enrollment / Screening	Baseline	Visualase Procedure	Follow-Up Visit 1 (14 day)	Follow-Up Visit 2 (3 mo)	Follow-Up Visit 3 (6 mo)	Follow-Up Visit 4 (12 mo)	Unscheduled Visit
Site Data Collection								
Informed Consent, Demographics	X							
Seizure Classification Form	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Epilepsy History	X							
Surgical Plan	X							
Medical History	X							
Medications	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
VNS Setting	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Eligibility Criteria, Pregnancy Test	X		X[1]					
EEG and Additional Testing	X							
MRI	X	X	X			X		
Pre-Surgical Evaluation Submission	X							
Neurological Exam		X		X	X	X	X	
Neuro-ophthalmologic Exam		X[4]			X[4]	X[4]	X[4]	X[4]
Neuropsych + QOL		X				X	X	
Seizure Diary Summary, Seizure Log		X[1]	X[1]	X	X	X	X	
Visualase Procedure, Product Disposition			X					
Procedure Steroid Log			X[1]					
Study Visit[2]		X[2]		X	X	X	X[2]	
NRS Pain Scale			X[3]					
Retreatment Submission								X[1]
Secondary Procedure								X[1]
Healthcare Services Utilization			X	X[1]	X[1]	X[1]	X[1]	X[1]
Study Exit		X[1]	X[1]	X[1]	X[1]	X[1]	X	X[1]
Adverse Event	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Device Deficiency			X[1]					
Protocol Deviation	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	

Case Report Forms	Enrollment / Screening	Baseline	Visualase Procedure	Follow-Up Visit 1 (14 day)	Follow-Up Visit 2 (3 mo)	Follow-Up Visit 3 (6 mo)	Follow-Up Visit 4 (12 mo)	Unscheduled Visit
Committee/Core Lab Evaluation Data Collection								
Pre-Surgical Evaluation	X							
Retreatment Evaluation								X[1]
Volumetric Analysis						X		
Neuropsych + QOL Analysis		X				X	X	
Neuro-ophthalmologic Analysis		X[4]			X[4]	X[4]	X[4]	X[4]

[1]If applicable, events, changes or updates should be captured on eCRFs as they occur.
[2]Including assessment of driving and employment/school status
[3]Pain scale will be completed after the Visualase procedure but prior to discharge.
[4]Neuro-ophthalmologic exam data should be entered for subjects as specified in Table 2.

7.9 Patient Informed Consent Process

A patient informed consent form (ICF) is a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining a signed ICF and an authorization to use and disclose personal health information (HIPAA release authorization) that has been signed and dated by the subject.

Prior to enrolling subjects, each site's IRB will be required to approve the ICF. The document(s) must be controlled (i.e., versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB. Any adaptation of the sample consent form must be reviewed and approved by Medtronic prior to enrolling subjects.

The Investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

The informed consent process must be conducted by the Principal Investigator or an authorized designee, and the ICF and authorization to use and disclose personal health information must be rendered to the subject in a language he/she is able to read and understand. The process of subject informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the Investigator or other site personnel. The informed consent process must not waive or appear to waive a subject's legal right. The language used must be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

If applicable, the witness must also sign and personally date the consent form to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given.

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the ICF must be signed and personally dated by the subject and Investigator or authorized designee. Consent by legally authorized representatives is not permitted, since the study requires the subject to complete seizure diaries and self-reported quality of life and mood assessments.

A copy of the signed and dated ICF and the authorization to use and disclose personal health information must be provided to the subject.

If consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

The original of the signed ICF must be filed in the hospital/clinical chart or with the subject's study documents.

CIP 4.0 includes the addition of neuro-ophthalmologic exams. Subjects consented but not yet treated with Visualase prior to CIP 4.0 will be asked to reconsent to these exams. Subjects who refuse to consent to CIP 4.0 will be withdrawn from the study.

Subjects treated with Visualase prior to CIP 4.0 will be asked to reconsent to have a neuro-ophthalmologic exam performed at their next scheduled study visit. Subjects who refuse to consent under CIP 4.0 will be followed under the protocol version to which they consented.

7.10 Enrollment

Upon signing the ICF, a subject is considered to be enrolled in the study. Each subject will be assigned a subject identification code (subject ID) that will be used on all documentation for the subject.

Each investigational site must maintain a log of all the subjects enrolled in the study, linking subject IDs to their names or medical record numbers.

The following activity will be completed at enrollment:

- Informed consent

7.11 Screening

The following must be completed at screening to assess subject eligibility:

- Review of demographics
- Review of medical history, including MRI and video EEG (and Wada test, functional MRI, magnetoencephalography [MEG], positron emission tomography [PET] and/or single-photon emission computerized tomography [SPECT] scans if available)
    - If the MRI on record shows evidence of eligibility for the study but was not completed within the protocol-defined timeframe, the Baseline Research MRI scan (see Baseline Visit) may be used to confirm eligibility.

Multiplanar reformatting (MPR) may be required to achieve the planes appropriate for eligibility verification.

- Review and documentation of epilepsy and seizure history, including seizure frequency during the 12 months immediately preceding enrollment, as ascertained by subject and family report, and/or seizure diaries from the medical record
- Review of past and current AEDs and current concomitant psychotropic medications
- Pregnancy test for women of childbearing potential

If results of the following assessment performed within 12 months of enrollment are not in the subject's medical record, they must be completed as part of screening:

- IQ Test: Wechsler Abbreviated Scale of Intelligence® (WASI® or WASI®-II) or Wechsler Adult Intelligence Scale Full Scale IQ or General Ability Index (WAIS®-III or WAIS®-IV FSIQ or GAI)
    - WASI-II materials will be provided by Medtronic as needed

After consent and prior to evaluation by the Pre-Surgical Evaluation Committee, the following activities will be completed:

- Subject provided a seizure diary
- Seizure classification

Subjects who sign an ICF but do not meet the eligibility criteria prior to the Visualase procedure, fail pre-surgical evaluation, or decline study participation will be considered screen failures.

7.12 Pre-Surgical Evaluation

The pre-surgical evaluation will consist of a central review of each subject's epilepsy history, MRI, EEG and any additional testing results available (e.g., PET, SPECT, invasive EEG or MEG) to confirm study qualification for the Visualase procedure.

Following consent, the site will enter subject data obtained during screening into the electronic database. The following data are specifically required for the pre-surgical evaluation for every enrolled subject (unless withdrawn prior to pre-surgical evaluation):

- MRI
    - T1- and T2-weighted images including thin section coronal images suitable for quantitative measurement, sufficient to confirm eligibility criteria
    - MRI report
- Video EEG
    - Printout of seizure activity from EEG
    - EEG report and video description
- Additional testing, if performed (e.g., PET, SPECT, invasive EEG or MEG)
- Epilepsy History and Seizure Classification Forms

Each subject's data are reviewed by a central committee (Appendix B) to verify study qualification for the Visualase procedure based on the following criteria:

- Does the submitted MRI show mesial temporal atrophy accompanied by either increased signal indicative of gliosis or by loss of internal architecture in the hippocampus?
- Does the EEG evidence show seizures from one temporal lobe consistent with MTLE?
- Is the seizure semiology consistent with MTLE?
- Based on the MRI, EEG and semiology, is the laterality consistent?
- If additional testing has been performed (e.g., PET, SPECT, invasive EEG or MEG), is it discordant from the seizure focus scheduled for ablation?

Each subject's data review will be assigned to one of the Committee members based on availability. The assigned Committee member may consult with others, though the assigned Committee member is individually responsible for making an evaluation decision. Committee members who also act as study investigators may not evaluate subjects enrolled by their own institution. The assigned Committee member will approve, disapprove or defer the subject's continued participation in the trial.

Subjects who are being considered for retreatment with another Visualase procedure (per Section 7.17) are evaluated by the committee per the same workflow as described above, though the supportive evidence requirements and verification criteria are determined on a case-by-case basis by the assigned Committee member (i.e., they are not pre-specified).

7.13 Baseline Visit

At any time after enrollment, but before the Visualase procedure, subjects will have a Baseline Visit to perform assessments that serve as a comparison to post Visualase procedure assessments. If needed, the Baseline Visit may be performed on multiple days, provided that all assessments are completed prior to the Visualase procedure.

The following activities are to be performed at this visit:

- Review and documentation of current AEDs and concomitant psychotropic medications
    - AEDs and dosages must remain stable for at least 30 days prior to the Visualase procedure
- Neurological exam, including oculomotor nerves and confrontation visual field test
- AE assessment
- Neurocognitive assessments, administered by qualified study personnel:
    - Boston Naming Test
    - Controlled Oral Word Association Test (COWA) (FAS)
    - Emory Semantic Fluency Tasks
    - Emory Famous Faces Naming/Recognition
    - Rey Auditory Verbal Learning Test, Form A
    - Wechsler Memory Scale (WMS-IV) Visual Reproduction Test
    - Wechsler Memory Scale (WMS-IV) Verbal Paired Associates

- Mood and Quality of Life (QOL) surveys, completed by the subject:
    - Beck Depression Inventory II
    - Beck Anxiety Inventory
    - Quality of Life in Epilepsy Inventory (QOLIE-31)
    - SF-36 Health Survey (SF-36)
    - Seizure Severity Questionnaire (SSQ) Version 3
- If available, seizure diary review and documentation of all seizures; a new diary may be given to subject to record future seizures
- Classification of any new types of seizures reported
- Research MRI scan per Section 7.6
    - MRI scans done within 12 months prior to enrollment and performed per Section 7.6 may be used for baseline.
- Assessment of driving and employment/school status
- Neuro-ophthalmologic exam (does not apply to subjects who have undergone the Visualase procedure prior to release of CIP 4.0)
    - Neuro-ophthalmologic exams performed within 12 months prior to enrollment and performed per Section 7.7 may be used for baseline

Results of neurological exams and neurocognitive assessments performed within 12 months prior to enrollment may be used for baseline.

7.14 Study Intervention: Visualase Procedure

The following activities are to be performed before the Visualase procedure:

- AEDs and dosages must remain stable for 30 days prior to the Visualase procedure.
- For females of childbearing potential, a repeat pregnancy test should be done within 7 days prior to the Visualase procedure to confirm the subject is still eligible. If the pregnancy test is positive, the subject is considered a screen failure and is exited from the study.

The following activities are to be performed prior to discharge:

- Visualase procedure
- MRI scans before, during and after the Visualase procedure (per Section 7.6)
- Review and documentation of current AEDs and concomitant psychotropic medications
- AE assessment
- Healthcare services utilization assessment
- If available, review of seizure diary and documentation of all seizures; new diary may be given to subject to record any future seizures
- Classification of any new seizure types reported
- Pain scale completed after the Visualase procedure

The procedure should be performed in accordance with the Instructions for Use (IFU) supplied with the device. A supplemental surgical Technique Recommendations document will be provided to all sites to facilitate consistent use, correct placement and

function of the device, as well as to minimize risk to subjects. The Technique Recommendations should be reviewed by all participating study surgeons and adherence to its guidance is strongly encouraged.

As indicated in the IFU, the potential effect of laser ablation on the stability of gadolinium complexes such as those used in MRI contrast agents (CAs) is currently unknown. Physicians should therefore observe a “washout” interval of at least three (3) half-lives (t½ for the CA being used) between the administration of Gadolinium-based CAs and initiation of the laser ablation.

The subject is positioned and stereotactic registration for intraoperative navigation and cranial access is accomplished. This may require application of a stereotactic head frame or it may be frameless via surface-based registration (e.g., facial tracing) or placement of scalp or bone fiducials. Other appropriate neurosurgical stereotactic modalities may be used in accordance with the manufacturer’s instructions. In cases where a head frame is used, imaging studies (CT or MRI) are then obtained and interpreted for usability by the surgeon, for identification of reference points and direct use in operative planning after the images are fused. At the surgeon's discretion, general anesthesia may be induced prior to application of the head frame. For all types of stereotactic registration, planning is performed to identify the precise entry point on the skull as well as to define the target and the safest trajectory through the brain to reach it, as follows. A target point is selected on a coronal MRI slice through the hippocampal head, within the center of the hippocampus from medial-to-lateral as well as dorsal-ventral (essentially the dentate gyrus). An initial entry point is selected on a coronal MRI slice through the hippocampal body at approximately the level of the lateral mesencephalic sulcus, which again is centered in the middle of the hippocampus. This trajectory is then expanded to the amygdala anteriorly, and to the cortical surface posteriorly. The defined trajectory is then further refined a) to maximize its extent within the hippocampus along its length from the level of the tectal plate to the amgydala; and b) to avoid cerebral vasculature and, if possible, entry into the ventricle. Attention is paid to the location of the optic radiation and thalamus to avoid proximity. Depending on the registration system, trajectory and target testing may be performed on the back table using a phantom.

If not previously performed, general anesthesia is induced. The subject’s head is prepped by shaving or parting the hair to achieve a sterile field. If a head frame is used, the stereotactic arc is attached to the existing stereotactic frame and the entry and target coordinates are input. Alternately, for frameless access, the stereotactic arm is mounted onto a skull clamp on the subject's head. The entry point is marked and, following local anesthesia, a scalp incision is performed and a minimally invasive twist drill craniostomy is made through the skull. The dura is then opened, for example using a sequence of sharp and blunt instruments or cautery. The pia is opened using similar techniques. With aid of an alignment rod, the laser anchor bolt is then placed through the twist drill craniostomy and secured into the skull at the correct trajectory.

After measurements associated with the trajectory from bone anchor to target are taken, the laser applicator probe is then advanced to the target site and held in place by the anchor bolt. If using a stereotactic head frame, the arc is then removed. If using frameless registration, the stereotactic arm and skull clamp are removed.

The subject is then prepared for transfer to the MRI suite to localize the laser applicator probe and perform the ablation of the brain tissue. During transfer, the laser application probe and the anchor bolt are managed to ensure the anchor bolt is secure and the

probe is not damaged. Alternately, the procedure may be performed in an MRI-equipped operative suite.

The subject is positioned within the MRI machine, with continued attention to the laser application probe and anchor bolt. An MRI scan is performed and interpreted by the surgeon to localize the laser application probe, confirming that the laser application probe is in the correct position and assessing for any adverse events during insertion or transfer.

The correct ablation parameters (power and duration) are determined by the surgeon. Selected MRI images are transferred to the ablation system and safety set points are identified on the images to define the area of ablation to prevent overheating of adjacent tissues and critical structures. Additional safety set points are placed on the images to monitor for excessive heating at the site of the laser application probe.

A test MRI-guided laser ablation is performed. After the test laser ablation is successfully completed, the MRI-guided laser ablation is performed at a wattage to achieve cell death. During ablation, the surgeon monitors and interprets MRI images superimposed on real-time thermal maps displaying the distribution of the heat, to ensure safety and successful target treatment. Based on the MRI information, it is frequently necessary to reposition the laser application probe several times and repeat the laser ablation.

At the end of the laser ablation surgery, a final gadolinium-enhanced MRI is acquired. The surgeon interprets the image to assess the ablation and confirm the ablation zone.

In the MRI suite or operating room, the laser application probe and the anchor bolt are removed. If a stereotactic head frame or bone fiducials were used, they are removed. The scalp incision site is closed by suture, staple, or glue. The subject is transported to the recovery room.

Procedures aborted prior to skin incision may be rescheduled. Procedures aborted after skin incision may be retreated per Section 7.17. If a procedure is aborted without plans to reschedule a subsequent Visualase procedure, the subject will be followed for the modified intent-to-treat analysis of seizures and AEs.

7.15 Scheduled Follow-up Visits

All follow-up visit windows will be calculated from the date of the Visualase procedure. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses will include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit. Follow-up visit windows are listed in Table 5 and are based on days post-Visualase procedure.

Table 5: Follow-up Visit Windows

Study Follow-up Visit	Window (Calculated days post-procedure)		
	Window Start (days post-procedure)	Target (days post-procedure)	Window End (days post-procedure)
Follow-up Visit 1 (14 day)	7	14	21
Follow-up Visit 2 (3 month)	76	90	104
Follow-up Visit 3 (6 month)	150	180	210
Follow-up Visit 4 (12 month)	365	365	410

7.15.1 Follow-up Visit 1: 14 ± 7 Days Post Visualase Procedure

The following activities are to be performed at this visit:

- Documentation of any changes in AEDs and concomitant psychotropic medications
- Neurological exam, including oculomotor nerves and confrontation visual field test
- AE assessment
- Healthcare services utilization assessment
- Review of seizure diary and documentation of any seizures; new diary may be given to subject to record future seizures
- Seizure classification of any new types of seizures

7.15.2 Follow-up Visit 2: 3 Months (90 ± 14 Days) Post Visualase Procedure

The following activities are to be performed at this visit:

- Documentation of any changes in AEDs and concomitant psychotropic medications
- Neurological exam, including oculomotor nerves and confrontation visual field test
- AE assessment
- Healthcare services utilization assessment
- Review of seizure diary and documentation of any seizures; new diary given to subject to record future seizures
- Seizure classification of any new types of seizures
- Neuro-ophthalmologic exam (for subjects consented to CIP 4.0 prior to Follow-up Visit 2)
    - A neuro-ophthalmologic exam performed after the Visualase procedure but prior to reconsent may be used if it was performed per Section 7.7

7.15.3 Follow-up Visit 3: 6 Months (180 ± 30 Days) Post Visualase Procedure

The following activities are to be performed at this visit:

- Documentation of any changes in AEDs and concomitant psychotropic medications
- Neurological exam, including oculomotor nerves and confrontation visual field test
- AE assessment
- Healthcare services utilization assessment
- Neurocognitive assessments, administered by qualified study personnel:
    - Boston Naming Test
    - Controlled Oral Word Association Test (COWA) (FAS)
    - Emory Semantic Fluency Tasks
    - Emory Famous Faces Naming/Recognition
    - Rey Auditory Verbal Learning Test, Form GE-AB

    - Wechsler Memory Scale (WMS-IV) Visual Reproduction Test
- Mood, Quality of Life (QOL) and Seizure Severity surveys, completed by the subject:
    - Beck Depression Inventory II
    - Beck Anxiety Inventory
    - Quality of Life in Epilepsy Inventory (QOLIE-31)
    - SF-36 Health Survey (SF-36)
    - Seizure Severity Questionnaire (SSQ) Version 3
- Review of seizure diary and documentation of any seizures; new diary given to subject to record future seizures
- Seizure classification of any new types of seizures
- Research MRI scan per Section 7.6

  Note: the subject must be scanned on the same scanner at the Baseline visit and at the 6-month visit
- Neuro-ophthalmologic exam (for subjects who had an abnormal finding at Follow-up Visit 2, and for subjects consented to CIP 4.0 after Follow-up Visit 2 but prior to Follow-up Visit 3)
    - A neuro-ophthalmologic exam performed after the Visualase procedure but prior to reconsent may be used if it was performed per Section 7.7

7.15.4 Follow-up Visit 4: 12 Months (365 + 45 Days) Post Visualase Procedure

The following activities are to be performed at this visit:

- Review and documentation of current AEDs and concomitant psychotropic medications
- Neurological exam, including oculomotor nerves and confrontation visual field test
- AE assessment
- Healthcare services utilization assessment
- Neurocognitive assessments, administered by qualified study personnel:
    - Boston Naming Test
    - Controlled Oral Word Association Test (COWA) (FAS)
    - Emory Semantic Fluency Tasks
    - Emory Famous Faces Naming/Recognition
    - Rey Auditory Verbal Learning Test, Form A
    - Wechsler Memory Scale (WMS-IV) Visual Reproduction Test
    - Wechsler Memory Scale (WMS-IV) Verbal Paired Associates
- Mood, Quality of Life (QOL) and Seizure Severity surveys completed by the subject:
    - Beck Depression Inventory II
    - Beck Anxiety Inventory
    - Quality of Life in Epilepsy Inventory (QOLIE-31)
    - SF-36 Health Survey (SF-36)

    - Seizure Severity Questionnaire (SSQ) Version 3
- Review of seizure diary and documentation of any seizures
- Seizure classification of any new types of seizures
- Assessment of driving and employment/school status
- Neuro-ophthalmologic exam (for subjects who had an unresolved abnormal finding at a previous visit, and for subjects consented to CIP 4.0 after Follow-up Visit 3 but prior to Follow-up Visit 4)
    - A neuro-ophthalmologic exam performed after the Visualase procedure but prior to reconsent may be used if it was performed per Section 7.7

7.15.5 Telephone Follow-up

Any subjects who are unable to return in person for an office visit during the visit window may be contacted by phone as a last resort. This allows for identification of any AEs that have occurred, review of the subject's seizure diary, and documentation of any changes in medications since last contact. In this case, the seizure diary may be sent to the site via email, mail or fax. Details of the conversation (including the date and names of the person who conducted the call and with whom they spoke), and the reason for the inability of the visit to occur must be documented.

NOTE: A telephone follow-up is NOT the preferred method of follow-up, and every attempt should be made to have the subject return to the office for the follow-up visit. AEs that are noted at the time of this follow-up visit will be recorded on an AE CRF. A deviation form must be completed for any missed assessments.

7.16 Unscheduled Follow-up Visits

An unscheduled visit is defined as any visit not required by this study. When an unscheduled follow up visit occurs, the subject must be assessed for adverse events and healthcare utilizations per Section 7.18. AE and Healthcare Services Utilization eCRFs must be completed as appropriate. The following should be completed as possible/necessary at the visit:

- Documentation of any changes in AEDs and concomitant psychotropic medications
- Review of seizure diary and documentation of any seizures; new diary given to subject to record future seizures
- Seizure classification of any new types of seizures

A neuro-ophthalmologic exam should be performed for subjects who experience symptoms of a potential vision-related adverse event following the Visualase procedure. A neuro-ophthalmologic exam performed prior to reconsent to CIP 4.0 may be used, if the exam was performed per Section 7.7.

7.17 Retreatment

Subjects who fail to achieve Engel Class I seizure freedom or whose procedure could not be completed as intended prior to discharge may be evaluated for retreatment. Retreatment is defined as a subsequent Visualase procedure after the subject's discharge following the initial Visualase procedure, to treat MTLE ipsilateral to the initial Visualase procedure and also within the temporal lobe. If it is determined that the ablation of additional tissue within the original target site may improve the outcome, the

justification for retreatment and supporting evidence will be entered on an eCRF and submitted to the Pre-Surgical Evaluation Committee for assessment per Section 7.12. Justification and supporting evidence for consideration of retreatment may include, but is not limited to, EEG demonstrating interictal and ictal discharges from the same temporal lobe, MRI showing no other lesions, same type of seizure behavior and auras, and no evidence of extra-temporal lesions.

If the Pre-Surgical Evaluation Committee disagrees with the recommendation for retreatment, the subject may continue participation in the study per their original follow-up schedule without retreatment. Alternatively, the subject may be withdrawn from the study.

If the committee agrees with the recommendation for retreatment, the subject may be scheduled for an additional Visualase procedure. Retreated subjects will have the same assessments at the same intervals as they would for an initial procedure. The new follow-up visit windows will be calculated based on the date of the retreatment Visualase procedure.

Subjects retreated with Visualase after the subject's discharge from the original Visualase procedure will be considered to have failed the primary efficacy endpoint. However, their data will contribute to specified secondary [redacted] endpoints.

Subjects who undergo open resection after a Visualase procedure will be considered to have failed the primary efficacy endpoint. Seizure and AE data will be collected per the standard of care for the site.

Subjects who are retreated with Visualase or undergo open resection after a Visualase procedure will be followed for 12 months after the secondary procedure, or until the last enrolled subject completes Follow-up Visit 4 (12 months), whichever occurs first.

All subjects will be assessed for safety for the duration of their participation in this study, regardless of whether they are retreated.

7.18 Healthcare Services Utilization

To assess use of healthcare resources specifically associated with epilepsy and the Visualase procedure, healthcare services utilization information will be collected during the Visualase procedure and hospital stay, and for any AEs requiring healthcare resources. Healthcare services utilization related to epilepsy and/or the Visualase procedure includes length of hospital stay, length of stay in ICU, ER visits, AEDs and psychotropic medications, physician office visits, and hospital readmissions.

7.19 Study Exit

A study exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing device-related, anesthesia-related, and/or procedure-related AEs are resolved or unresolved with no further actions planned. Upon exiting from the study, no further study data will be collected and no further study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Subject has completed follow-up
- Subject lost to follow-up

- Subject death
- Subject did not meet inclusion/exclusion criteria (If ineligibility is discovered after the Visualase procedure, the subject will still be followed through 12 months post procedure.)
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., the subject enrolls in a confounding investigational study, the subject fails to maintain adequate study compliance, or it is medically necessary or in the best interest of the subject)

The following information is required to be documented at study exit:

- Reason for exit
- Date of study exit
- If the subject is determined to be lost to follow-up, details of a minimum of 3 contact attempts via 2 different methods (e.g., email, phone, and/or certified letter) must be recorded.

7.20 Medications

All prescription medications for an epilepsy or psychiatric indication (including rescue medications as taken) will be recorded on an electronic medication log from the time of enrollment. Generic medication names and doses will be captured, and any changes will be recorded on the medication log.

AEDs and their doses should remain stable from 30 days prior to the procedure through the final visit. Transient weans of AEDs prior to the Visualase procedure are permitted for patient safety, and intravenous doses of AEDs during the procedure are permitted.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator.

AED changes will be evaluated per Section 14.3.4.

7.21 Role of the Sponsor Representatives

Sponsor representatives may provide support as required for the study, including:

- Study training relevant to the involvement of personnel conducting study activities and Investigator responsibilities
- Technical support during the Visualase procedure under the supervision of a study Investigator
- Intraoperative data collection support (e.g., acquisition of system logs and files from the Visualase workstation) under the supervision of a study Investigator, but no data entry will be performed by Medtronic personnel or their representatives at sites
- Monitoring and auditing activities

8 INVESTIGATIONAL DEVICE / EQUIPMENT STORAGE, HANDLING AND TRACEABILITY

The Visualase System comprises a laser energy source, a pump for circulating coolant through the applicator, a computer workstation (Visualase capital equipment), and a

cooled laser applicator system and optional neuro accessory kit (Visualase disposables). All components of the Visualase System are FDA-cleared for use in neurosurgical procedures.

As the Visualase System is commercially released, no special receipt, storage, or reconciliation requirements apply. Management of Visualase System inventories by investigational sites will be in accordance with their respective operating policies.

Visualase capital equipment and disposables will enter the accountability system when they are accessed/opened with the intent to be used within the context of the study, at which point they become “investigational devices.” Therefore, none of the Visualase capital equipment and disposables will be labelled as investigational, and the date they are accessed/opened with the intent to be used within the context of the study will be considered the date of receipt by the site.

For each Visualase disposable opened with the intent of being used within the context of the study, the following information will be documented:

- Model Number
- Lot number
- Date used/opened
- Subject ID
- Date returned/disposed
- Final disposition
- Reason for return/method of disposal
- Name/initials of the person who returned or disposed the device
- Quantity

For Visualase capital equipment, the following information will be documented:

- Model number
- Serial number
- Date installed
- Date returned/disposed (if applicable)
- Final disposition
- Reason for return/method of disposal
- Name/initials of the person who returned or disposed the device (if applicable)
- Quantity

Additionally, use and disposition of investigational devices will be documented and tracked on eCRFs.

The Sponsor will cover the cost of investigational disposables for study procedures.

9 STUDY DEVIATIONS

The investigator should not deviate from the CIP, except under emergency circumstances to protect the rights, safety or well-being of human subjects. A study deviation is defined as an event within a study that did not occur according to the CIP or the Clinical Trial Agreement, including, but not limited to, the following:

- Failure to obtain informed consent prior to participation in the study
- Incorrect version of the consent form rendered to the subject
- Failure to obtain IRB approval before conducting study-related activities

- Enrollment of subjects during lapse of IRB approval
- Investigator exceeding enrollment limits specified by Sponsor or IRB
- Treated subject did not meet inclusion/exclusion criteria.
- Subject did not attend follow-up visit (missed visit)
- Follow-up visit outside of the protocol-defined window
- Unauthorized use of an investigational product in the study by a physician who has not signed a Trial Agreement and/or whose training was not documented
- AE not reported by Investigator in the required regulatory timeframe

If a deviation involves a failure to obtain a subject's consent prior to use of an investigational device or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB policies and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Refer to Investigator Reports, Table 9 for deviation reporting requirements and timeframes for reporting to Medtronic.

All study deviations must be reported on an eCRF regardless of whether medically justifiable, an inadvertent occurrence, or taken to protect the subject in an emergency.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious Investigator compliance issues may result in initiation of a corrective action plan with the Investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the Investigator's participation in the study.

10 ADVERSE EVENTS AND DEVICE DEFICIENCIES

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

10.1 Adverse Event and Device Deficiency Definitions

Adverse event and device deficiency definitions are provided in Table 6. Where the definition indicates "device", it refers to any Visualase System component used in the study.

Table 6: Adverse Event Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. *(ISO 14155:2011, 3.2)* *NOTE: The specific adverse events collected for this study are described in Section 10.2.1*
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. *(ISO 14155:2011, 3.1)*
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling *(ISO 14155:2011, 3.15)*
Relatedness	
Device-Related	An adverse event that is directly related to the use, presence and/or performance of the Visualase System.
Procedure-Related	An adverse event that is not directly related to the Visualase System but is directly attributable to the surgical procedure in which Visualase was used. For the purpose of determining adverse event relatedness, the procedure begins at first scalp incision and ends at closure of all scalp incisions.
Anesthesia-Related	An adverse event that is not directly related to the Visualase System, nor to the Visualase procedure, but is directly attributable to the anesthesia for the Visualase procedure.
Epilepsy-Related	An adverse event related to the subject's epilepsy or AEDs.

Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. *(ISO 14155:2011, 3.37)*
Serious Adverse Device Effect	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. *(ISO 14155:2011, 3.36)*
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. *(21 CFR 812.3(s))*
Duration	
Transient	Short-lived, not permanent. For the purpose of this study, adverse events lasting 30 days or fewer are considered transient.
Prolonged	Continuing, persistent. For the purpose of this study, adverse events lasting more than 30 days but that do not meet the definition of permanent.
Permanent	Long-lasting, for a year or longer. For the purpose of this study, adverse events not resolved at study exit will be considered permanent.
Severity	
Mild	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. *(CDISC)*
Moderate	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. *(CDISC)*

<table>
<tr><td>Severe</td><td>A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. (CDISC)</td></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td>Pre-operative</td><td>An adverse event that occurs after the informed consent has been signed but before the first scalp incision for the Visualase procedure</td></tr>
<tr><td>Intra-operative</td><td>An adverse event that occurs during the Visualase procedure, after the first scalp incision and prior to completion of all scalp incision closures.</td></tr>
<tr><td>Post-operative</td><td>An adverse event that occurs after the Visualase procedure, after completion of all scalp incision closures.</td></tr>
<tr><td>Unavoidable Event

(These events need not be reported unless the event worsens or is present outside the stated timeframe post procedure.)</td><td>An event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator’s opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) Post Visualase Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48</td></tr>
<tr><td>Pain at incisional/access site</td><td>120</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168 (1 week)</td></tr>
<tr><td>Sleep problems or insomnia</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Pain/discomfort/stiffness related to immobilization during procedure</td><td>72</td></tr>
<tr><td>Periorbital edema related to stereotactic frame pin placement</td><td>72</td></tr>
<tr><td>Headache</td><td>168 (1 week)</td></tr>
<tr><td>Scalp pain</td><td>168 (1 week)</td></tr>
<tr><td>Scalp numbness</td><td>168 (1 week)</td></tr>
<tr><td>Blurry vision</td><td>336 (2 weeks)</td></tr>
<tr><td>Mild cerebral edema</td><td>1008 (6 weeks)</td></tr>
</table></td></tr>
<tr><td colspan="2">Death Classification</td></tr>
<tr><td>Sudden Unexpected Death in Epilepsy (SUDEP)</td><td>A sudden, unexpected death of someone with epilepsy, who was otherwise healthy. May be found lying face down and/or found dead in bed without having had a convulsive seizure. There may or may not be evidence of a seizure close to the time of death. The death is not known to be related to an accident or seizure emergency such as status epilepticus. If an autopsy is performed, no other of cause of death is found.[42]</td></tr>
</table>

10.2 Adverse Event and Device Deficiency Assessment

10.2.1 Study Reportable Adverse Events

Adverse event definitions are provided in Table 6. To ensure all AEs that are potentially relevant to the SLATE study are collected, the following adverse events will be collected and reported to Medtronic during the study, starting from the time the subject signs the informed consent:

- Device-related AEs
- Procedure-related AEs
- Anesthesia-related AEs
- Epilepsy-related AEs
- All SAEs

Each AE must be recorded on a separate AE eCRF and include a description of the event, the diagnosis, date of event onset, the date the site became aware of the event, diagnostic tests and procedures performed, actions taken as a result of the event, relatedness and severity of the event and the outcome of the event. Subject deaths are also required to be reported. Refer to Section 10.5 for subject death collection and reporting requirements.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Unavoidable events listed in Table 6 need not be reported unless the AE worsens or is present outside the stated timeframe post-procedure.

Seizures are inherent to the disease state of the target population of this study and are expected to continue in a portion of subjects after the Visualase procedure. While all seizures will be reported and captured in a seizure diary, they will not be reported as AEs unless there is a worsening in the nature, severity or degree of incidence, according to the Investigator's opinion. Following are examples of seizures that are reportable as AEs:

- Worsening in clinical manifestations (for example, subject began having falls with their seizures which was not previously a component)
- Seizure frequency is increased
- Subject experiences a new seizure type or non-epileptic seizure
- Seizure led to injury or death

Memory and naming decline are established risks following epilepsy surgery involving the temporal lobe. In standard ATL resections, changes in these cognitive scores are expected and consequently are not considered as adverse events unless the magnitude of change exceeds the site investigator's expectations.

This study employs a rigorous battery of neuropsychological tests to better characterize individual change in naming and memory following laser ablation. Changes in these cognitive scores are expected and consequently are not considered as adverse events unless the magnitude of change exceeds expectations by the site investigator.

Similarly, adverse events related to depression and anxiety will also be based on site investigator assessment, and a decline in mood assessment scores alone will not be considered an adverse event.

For AEs that require immediate reporting (see Table 9), initial reporting may be done by completing as much information as possible on an AE eCRF. The remainder of the AE eCRF must be completed as soon as possible.

10.2.2 Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic on a Device Deficiency eCRF. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an adverse event only.

Device deficiencies that did not lead to an AE should be reported as Device Deficiencies only and will be evaluated by the Investigator to determine if they could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate).

10.2.3 Adverse Event Updates and Resolution

For any changes in status of a previously reported AE (e.g., change in actions taken, change in outcome, change in relatedness or severity), an update to the original AE eCRF must be completed. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject exits the study, or until study closure, whichever occurs first.

If a subject is being considered for exit from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved procedure-related, anesthesia-related, or device-related AEs, as classified by the Investigator, are resolved or are unresolved with no further actions planned.

At the time of study exit, all AEs with an outcome of “Unresolved, further actions or treatment planned” must be reviewed by the Investigator, and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, severity, tests and procedures, or actions taken, the outcome must be updated to reflect “Unresolved at time of study closure.”

Reportable adverse events that may be deemed transient, prolonged, or permanent in nature (see Appendix F) and are unresolved when the subject exits the study will be considered permanent.

10.3 Adverse Event Classification and Device Deficiency Review and Reporting

All AEs and device deficiencies will be reviewed by a Medtronic representative for completeness and accuracy and will request clarification and/or additional information from the Investigator when necessary.

Adverse events will be classified according to the definitions provided in Table 6.

Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the Investigator.

Regulatory reporting of AEs will be completed according to FDA requirements. Refer to Section 10.4 for a list of required Investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the Investigator to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

Appendix E contains the Foreseeable Adverse Event List (FAL), which is a list of AEs related to the system or procedure that have been observed in previous relevant

(epilepsy) studies and may be experienced by subjects. This list may help to assess if an AE is unexpected in nature.

For emergency contact regarding a UADE, SAE and/or SADE, contact a clinical study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the contact information provided in this CIP).

AEs and deaths will be classified according to the responsibilities and parameters outlined in Table 7 below.

Table 7: Adverse Event Classification Responsibilities

What is Classified?	Who Classifies?	Classification Parameters
Timing of the Event	Investigator	Pre-operative, intra-operative or post-operative
Relatedness	Investigator	Procedure Anesthesia Device (Visualase System) Epilepsy
	Sponsor	Procedure Anesthesia Device (Visualase System) Epilepsy
Seriousness	Investigator	Serious adverse event
	Sponsor	Serious adverse event Unanticipated adverse device effect
Severity	Investigator	Mild, moderate, or severe
	Sponsor	Mild, moderate, or severe
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	SUDEP

10.4 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs will be completed according to FDA requirements. Refer to Table 8 for a list of required Investigator reporting requirements and timeframes, and of required Medtronic reporting requirements and timeframes.

The Investigator must submit to the Sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. Medtronic is also required to report these events to the FDA. It is the responsibility of the Investigator to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

10.5 Subject Death

The AE that led to the subject death must be documented on an Adverse Event form as soon as possible after the Investigator first learns of the death. A study exit eCRF must also be completed.

10.6 Product Complaint Reporting

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

Since all device components used in the SLATE study are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be performed in addition to the AE reporting requirements. Refer to FDA regulations (21 CFR Part 803) for reporting requirements.

11 RISK ANALYSIS

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk analysis process for the SLATE study was performed to ensure that the level of risk is acceptable prior to starting the clinical study.

Possible risks of the Visualase procedure in this study include, but are not limited to, the foreseeable adverse events listed in Appendix E. There may be other discomforts and risks related to the Visualase device and/or this study that are not foreseen at this time.

There is a possibility of risks to an unborn child. These risks are unknown. Women who are pregnant at the time of the procedure or plan to become pregnant during the course of the study are excluded from participating.

Possible additional risks associated with participation in the SLATE study include, but are not limited to, the following:

- Ineffective treatment:
    - Risks associated with continued seizures, including injury and sudden unexpected death in epilepsy (SUDEP)
- Neuropsychological testing:
    - Mild emotional stress
    - Embarrassment or unpleasant feelings
    - Mild emotional discomfort due to personal questions about mood or behavior
- Research MRI:
    - Bothersome MRI machine noise
    - Feelings of claustrophobia
    - Injury if objects containing iron or metal are present in the subject or anywhere in the room
- Research MRI contrast agent (gadolinium):
    - Discomfort

    - Tingling or warmth in the lips
    - Metallic taste in the mouth
    - Tingling in the arm
    - Nausea
    - Headache
    - Allergic reaction to gadolinium
- Visual field exam
    - Fatigue
- Neuro-ophthalmologic exam dilating eye drops
    - Stinging
    - Blurry vision
    - Sensitivity to light
    - Allergic reaction

11.1 Risk Minimization

The Visualase System is FDA-cleared for coagulation and necrotization in Neurosurgical procedures. It is used in this study as an unaltered, commercially-available medical device that is subject to Quality System Regulations and Good Manufacturing Practices per 21 CFR Part 820. A risk assessment for the device has been conducted by the manufacturer per ISO 14971 and is included as part of the Design History File that supports commercial use of the device. Appropriate mitigations to the application, design and manufacturing process related risks have been implemented.

While the Visualase System is cleared for use in soft tissue ablation in neurosurgical procedures, the specific use to treat epilepsy is considered investigational in this study. The following measures will be taken to further minimize the risks arising from participation in this study:

- The Sponsor will only involve Investigators and institutions who are experienced with the use of the Visualase System and the surgical procedures necessary to treat patients with MTLE
- Proper subject preoperative assessment, surgical care, and postoperative follow-up will be maintained to minimize the risk associated with study procedures
- The Visualase System will be used according to the Instructions for Use. Technique Recommendations for the SLATE study will be provided to all study surgeons.
- Sponsor representatives will be present during Visualase procedures for technical support
- An independent Data Monitoring Committee (Appendix D) will review AEs and aggregate clinical study data in order to make recommendations regarding study conduct, should safety concerns be identified
- Only subjects who meet appropriate study inclusion and exclusion criteria will be selected
- The Sponsor will only involve Investigators and institutions who are qualified by training and experience to conduct clinical research

11.2 Potential Benefits

The Visualase System is indicated for use to necrotize or coagulate tissue in Neurosurgical procedures. Although no assurances or guarantees can be made, there is a reasonable expectation that laser ablation of epileptogenic foci in patients with MTLE may result in seizure freedom or reduction in seizure frequency or severity. Seizure control is expected to yield improvements in health-related quality of life and reduce the risks of seizure-related injury and sudden unexplained death in epilepsy. Other potential benefits include providing subjects with a less invasive treatment option, potentially reducing time to return to normal activities and the risks of open resective surgery such as neuropsychological defects.[20-29]

The information gained from this study could result in the improved management of MTLE. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

11.3 Risk-to-Benefit Analysis

Although there are risks affiliated with involvement in this study, as there are with any intracranial surgical procedure, it is believed that for properly selected subjects the potential benefits outweigh the risks.

As the Visualase System is indicated for use in neurosurgical procedures, investigational sites may offer laser ablation for MTLE patients outside of this study. For patients who would otherwise choose laser ablation regardless of study participation, the additional risks of participating in this study are not materially different, and the medical benefits are no greater than seeking the same treatment outside of the study.

12 MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' medical histories (clinic and hospital records, and other source data/documentation) upon request as per the subject informed consent form, HIPAA release authorization, and Clinical Trial Agreement. The Principal Investigator should also be available during monitoring visits.

12.1 Monitoring Visits

Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular site.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, site study compliance, number of AEs, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study site. Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

13 PLANNED STUDY CLOSURE, EARLY TERMINATION OR STUDY SUSPENSION

13.1 Planned Study Closure

Study closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the final report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete. Refer to Section 7.19 for additional information regarding study exit procedures. Medical care may be provided by the treating physician per the site's standard of care after study closure.

13.2 Early Termination or Suspension

Early termination of the study is defined as the closure of the clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site.

13.2.1 Study-wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- AEs associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance is different from the product's design intent
- Decision by Medtronic or FDA
- Recommendation of early termination by the DMC

13.2.2 Investigator/Site Termination or Suspension

Possible reasons for clinical Investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval, failure to obtain annual renewal of IRB approval of the study, or IRB suspension of the site or Investigator
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g., failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.) or persistent non-compliance to the clinical investigation (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

13.3 Procedures for Termination or Suspension

13.3.1 Medtronic-initiated and Regulatory Authority-initiated

- In the case of study suspension or termination, Medtronic will promptly inform the clinical Investigators and provide the reasons for termination or suspension. If the termination or suspension is Medtronic-initiated, Medtronic will also inform the FDA.
- In the case of study termination, the Investigator must inform the subjects
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare
- In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the Investigator or Medtronic will promptly inform the IRB

13.3.2 Investigator-initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The Investigator will promptly inform the institution (if required)
- The Investigator will promptly inform the IRB
- The Investigator will promptly inform the subjects
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

13.3.3 IRB-initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is involved
- The Investigator will inform his/her institution (if required)
- The Investigator will promptly inform the subjects, with the rationale for the study termination or suspension

14 STATISTICAL METHODS AND DATA ANALYSIS

14.1 Sample Size Determination

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.

The primary efficacy endpoint is the 12-month seizure-free rate. The analysis of the primary efficacy endpoint will include a point estimate and exact 95% confidence interval (CI) of the rate. The lower bound of the 95% CI of the seizure freedom rate following the Visualase procedure must be above 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 these assumptions, 89% power can be achieved with data from 150 treated subjects.

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.

14.2 General Considerations

Statistical analyses will be performed using SAS Software, Version 9.4 or later.

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

A Statistical Analysis Plan (SAP) will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

14.3 Analysis Populations

14.3.1 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.

14.3.2 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. Missing primary and secondary efficacy endpoints that are testable will be imputed. Imputation for the specified secondary cognitive and QOL efficacy endpoints will only include the English language version subset.

14.3.3 [redacted]

[redacted]

14.3.4 [redacted]

[redacted]

14.4 Primary Safety Endpoint

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

14.4.1 Hypothesis

It is hypothesized that the upper bound of the 95% confidence interval for the proportion of subjects experiencing any qualifying device-, procedure-, or anesthesia-related adverse events (per Appendix F) through 12 months following the Visualase procedure will be less than 40%.

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.

14.4.2 Performance Requirements

The performance criteria of an AE rate of 40% is based on the analysis by Attiah et al.[30]

14.4.3 Analysis Methods

An exact 95% confidence interval (Clopper[43]) will be calculated to determine if the upper bound of the CI for qualified AEs is less than 40%.

14.5 Primary Efficacy Endpoint

The primary efficacy endpoint is seizure freedom (defined as Engel Class I, Appendix C) 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).

14.5.1 Hypothesis

It is hypothesized that the lower bound of the 95% confidence interval for seizure freedom at 12 months following the Visualase procedure will be greater than 43%.

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% confidence interval 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%.

14.5.2 Performance Requirements

The performance criterion of seizure-free percentage greater than 43% is based on the analysis by Attiah et al.[30]

14.5.3 Analysis Methods

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

14.6 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 order using an alpha of 0.05 and will stop if any test fails to reach significance.

14.6.1 Secondary Endpoint #1

Seizure freedom (defined as Engel Class I, Appendix C) at 12 months following the Visualase procedure compared to historical control 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.

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% confidence interval for the percentage of subjects who are seizure free will be calculated.

14.6.2 Secondary Endpoint #2

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

It is hypothesized that the lower bound of the 95% confidence interval for seizure freedom at 12 months following the Visualase procedure, including subjects retreated with Visualase (per Section 7.17), 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.

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% confidence interval 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%.

14.6.3 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.

Null Hypothesis: $\mu (V\text{-}BNT - BSL\text{-}BNT) + \delta \leq 0$
Alternate Hypothesis: $\mu (V\text{-}BNT - BSL\text{-}BNT) + \delta > 0$

Where $\mu (V\text{-}BNT - BSL\text{-}BNT)$ = 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.[44] A two-tailed alpha of 0.05 will be used.

14.6.4 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.

Null Hypothesis: $\mu (V\text{-}RAVLT - BSL\text{-}RAVLT) + \delta \leq 0$
Alternate Hypothesis: $\mu (V\text{-}RAVLT - BSL\text{-}RAVLT) + \delta > 0$

Where $\mu (V\text{-}RAVLT - BSL\text{-}RAVLT)$ = 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.[44] A two-tailed alpha of 0.05 will be used.

14.6.5 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.

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.[45]

14.6.6 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.

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.[45]

14.6.7 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.

Null Hypothesis: M (V-SF-36-PCS - BSL-SF-36-PCS) ≤ 0
Alternate Hypothesis: M (V-SF-36-PCS - BSL-SF-36-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.[45]

14.6.8 Secondary Endpoint #8

Seizure freedom (defined as Engel Class I, Appendix C) at 12 months following the Visualase procedure compared to historical control 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.

Null Hypothesis: π (V-SF – 64%) + $\delta \leq 0$
Alternate Hypothesis: π (V-SF – 64%) + $\delta > 0$

Where π (V-SF – 64%) is the proportion of subjects treated with Visualase experiencing no seizures.

An exact 95% confidence interval 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%.

14.7 [redacted]

[redacted]

14.8 Interim Analysis

No formal interim analysis is planned. Any unplanned interim analyses will be conducted under the auspices of the DMC assigned to this study. The DMC is authorized to review interim efficacy and safety analyses and, if necessary, to disseminate those results. The DMC will release interim results only 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.

14.9 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. The primary method of imputation will be by multiple imputation (SAS PROC MI and MIANALIZE) using the Markov chain Monte Carlo method. Details of predictor variables to be used in SAS PROC MI, seed number, and number of imputations to be performed will be provided in the SAP. [redacted]

14.10 [redacted]

[redacted]

[redacted]

15 DATA AND QUALITY MANAGEMENT

15.1 Documentation Confidentiality and Accessibility

Documentation provided and generated as a result of this study is considered confidential and governed by the terms of the Confidentiality and Study Agreements. Access to and collection of medical records and subject data for this study is governed by the terms of the ICF and HIPAA release authorization.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous.

The Sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical Investigator(s)/institution(s) must allow study-related monitoring, audits, IRB review and regulatory inspection by providing direct access to source data/documents.

15.2 Data Collection

Data will be collected using an electronic data management system for clinical trials. The electronic data management system will be compliant with the provisions in the Code of Federal Regulations Title 21 Part 11 for Electronic Records. Electronic CRF data will be stored in a secure, password-protected database which will be backed up routinely. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress, including subject compliance.

At the end of the study, the data will be frozen and will be retained per Medtronic policies. The data reported on the eCRFs must be derived from source documents and be consistent with these source documents, and any discrepancies must be explained in writing.

15.3 Study Documentation

The Sponsor is responsible for the development, distribution, maintenance and long-term storage of study documentation. Pre-study documentation includes the core study protocol, CRF templates, CRF instructions, visual aids, and other study-specific materials. Intra- and post-study documentation includes archived versions of study protocols, CRF templates, original completed CRFs, CRF instructions, visual aids, source documents and other study-specific materials.

The data reported on eCRFs must be derived from source documents and be consistent with these source documents. Any discrepancies must be explained in writing.

15.4 Data Flow

Investigational sites are responsible for notifying the Sponsor of new subject enrollments using the appropriate notification system. Notice to the Sponsor of the entry of a subject in the study is the indicator that data will be expected at the intervals prescribed in this protocol.

15.5 Data Transmission and Entry

Data will be entered into the database at the intervals prescribed in this CIP (Section 7.7). Completed eCRFs and required file uploads will be forwarded to the Sponsor, or their designee.

15.6 Data Edits

Data edits will be performed using industry recognized methods, for which an acceptable audit trail exists to record all data alterations. As required, all queries for data verification/correction will be completed by the designated study personnel and include approval by the Investigator. The data editing process includes, but may not be limited to:

- Review of the CRFs will be conducted by the Sponsor, and manual edit checks may be added
- The Data Manager will check for discrepancies that can be corrected using Global Rule
- Automated edit checks will fire upon data entry, generating Data Clarification Forms (DCFs) for site verification/correction
- At periodic intervals, data validation activities will be performed to assess the completeness and accuracy of the data
- Clean and frozen data will be translated into the appropriate file type for data analysis

15.7 Electronic Medical Records

For sites using electronic medical records, the Sponsor may request that the study site designee print original source documents and verify that the record is a true reproduction of the original source document by initialling and dating the hard copy. Any discrepancies must be explained in writing.

16 REQUIRED RECORDS AND REPORTS

16.1 Investigator Records

The Investigator is responsible for the preparation and retention of the records cited below. All of the records listed below, with the exception of case history records and CRFs, should be kept in the Investigator site file or subject study binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period

of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting a pre-market approval application. Medtronic requires notification in writing if the Investigator wishes to store study documents off-site or to relinquish the study data records so that mutually agreed-upon arrangements can be made for transfer of the data records to a suitably qualified, responsible person.

- All correspondence between the IRB, sponsor, monitor, FDA, and the Investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
    - Informed consent form signed and dated by subject and Investigator or designee
    - Observations of AEs/ADEs/device deficiencies
    - Medical history
    - Visualase procedure and follow-up data
    - Documentation of the dates and rationale for any deviation from the protocol
- Financial disclosure
- Subject log
- All approved versions of the CIP, ICF, and Report of Prior Investigations Summary
- Signed and dated Investigator agreement
- Current curriculum vitae of principal investigators and key members of investigational site team
- Documentation of delegated tasks
- IRB approval documentation. Written information that the Investigator or other study staff, when member of the IRB, did not participate in the approval process
- Study training records for site staff
- Any other records that FDA requires to be maintained (e.g., financial disclosure)
- Final Study Report including the statistical analysis

16.2 Investigator Reports

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all CRFs, AEs, device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

The Investigator must prepare and submit in a complete, accurate, and timely manner the reports listed in this section.

Table 8: Investigator Reports per FDA Regulations

Report	Submit to	Description/Timing
UADE	Sponsor and IRB	The Investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. *(21 CFR 812.150(a)(1))*
Withdrawal of IRB Approval (either suspension or termination)	Sponsor	The Investigator shall report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*
Progress Report	Sponsor and IRB	The Investigator shall submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*.
Study Deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan. If these changes or deviations may affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, FDA and IRB must also be notified. *(21 CFR 812.150(a)(4))*
Failure to Obtain Informed Consent (prior to investigational device use)	Sponsor and IRB	If an Investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final Report	Sponsor and IRB	This report shall be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB and FDA	An Investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

16.3 Sponsor Records

Medtronic must maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Signed Investigator agreements, financial disclosure and current curriculum vitae of Principal Investigator and key members of the investigational site team
- Delegated task list
- All signed and dated CRFs submitted by Investigator, including reports of AEs, ADEs and device deficiencies

- All approved informed consent templates and other information provided to the subjects as well as advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- FDA correspondence, notification and approval
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The CIP, Report of Prior Investigations Summary and study related reports, and revisions
- Study training records for site personnel and Medtronic personnel involved in the study

16.4 Sponsor Reports

Medtronic must prepare and submit the following complete, accurate, and timely reports listed in Table 9 below. In addition to the reports listed below, Medtronic must, upon request of reviewing IRB or FDA, provide accurate, complete and current information about any aspect of the investigation.

Table 9: Sponsor Reports

Report	Submit to	Description/Constraints
UADE	FDA, IRBs, and Investigators	A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.
Withdrawal of IRB Approval	FDA, IRBs, and Investigators	A sponsor shall notify FDA and all reviewing IRBs and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval *(21 CFR 812.150(b)(2))*
Withdrawal of FDA Approval	IRBs and Investigators	A sponsor shall notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	A sponsor shall submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	IRBs and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*

Report	Submit to	Description/Constraints
Recall and Device Disposition	FDA and IRBs	A sponsor shall notify FDA and all reviewing IRBs any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made. *(21 CFR 812.150(b)(6))*
Final Report	FDA, IRBs, and Investigators	The sponsor shall notify FDA within 30 working days of the completion or termination of the investigation. The sponsor shall submit a final report to the FDA, investigators, and all IRBs within 6 months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Failure to Obtain Informed Consent (prior to investigational device use)	FDA	Investigator's report of use of investigational device without obtaining consent will be submitted to FDA within 5 working days of notification. *(21 CFR 812.150(b)(8))*
Study Deviation	Investigators	Ensure that all deviations from the Clinical Investigational Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations may be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports per standard operating procedure.

Appendix A: Bibliography

Reference List

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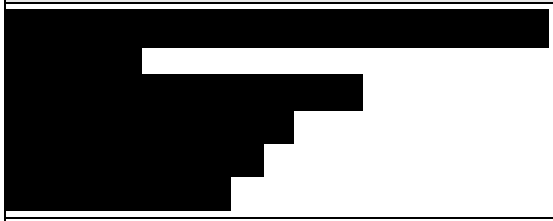
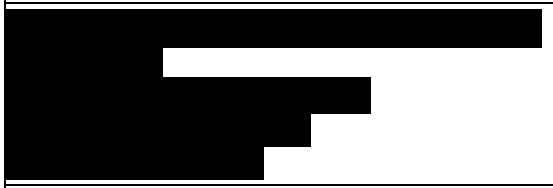
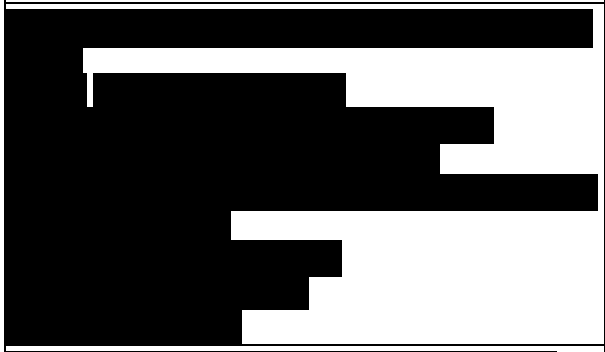
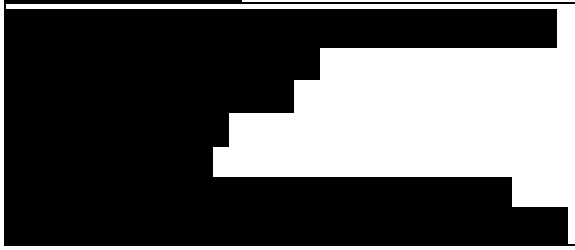
Appendix B: Clinical Research Organizations, Central Reviewers and Core Labs

Clinical Research Organizations (CROs) will be used to develop and manage the study's eCRF database, and to provide statistical support of data analysis. Contact information and duties performed are listed below.

To standardize critical assessments during the study, in addition to site reported results, assessments will be made by central reviewers or core labs as listed below. Assessments will be conducted in accordance with the respective reviewers'/core labs' charters and/or instructions.

Contact Information	Duties performed
	• Develop study electronic case report forms, edit checks, and study management reports • Review electronic case report forms, manage discrepancies, and code deviations
	• Provide statistical recommendations for study endpoints and analysis • Generate statistical reports throughout the study
	• Provide site training and uniform scoring on neuropsychological assessment battery • Monitor neuropsychological data quality • Analyze neuroimaging data by volumetric analysis and visual inspection
	• Review subjects' epilepsy history, MRI, EEG and additional testing, if performed (e.g., PET, SPECT, invasive EEG or MEG) to confirm study qualification for the Visualase procedure • Approve, disapprove or defer the subject's continued participation in the trial.

Any changes or additions to the clinical research organizations, central reviewers, or core lab information may be provided in a separate document.

Appendix C: 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.

[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

Appendix D: Data Monitoring Committee (DMC)

Point	Examples
DMC will be used	Ongoing oversight for this study will be provided by an independent Data Monitoring Committee (DMC).
Who will be involved	The DMC will have one statistician, at least one physician specializing in neurosurgery, at least one physician specializing in neurology, and one neuropsychologist. None of the DMC members are participating in the SLATE study. A chairperson from among those members will be identified.
Responsibility of the DMC	The DMC will be responsible for the following: ○ Monitoring subject safety through review of aggregate clinical study data and adverse events ○ Acting as an advisory panel on study design, study materials, study conduct, and subject safety issues ○ Ensuring continued scientific validity and necessity, and making recommendations for protocol modifications ○ Investigating root cause of missing data to minimize potential bias (i.e., screen failures, lost-to-follow-up, discontinuation from treatment) ○ Evaluating issues associated with the procedural aspects of the clinical trial (e.g., slow enrollment) and providing recommendations for their resolution
Recommendations	The DMC will be advisory to the sponsor. The DMC may provide recommendations for continuation of the study, or early termination due to futility or safety concerns, or early attainment of study objectives. NOTE: Approval to proceed with the study or discontinue the study must be determined by a consensus of the DMC

A DMC charter will be developed prior to the first subject enrollment.

The DMC will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for safety data review, chairman appointment, and guidelines for study recommendations. The DMC will meet on a periodic basis to perform data review, including at a minimum, all SAEs and deaths, and will meet more frequently when needed. DMC meetings may consist of both open and closed sessions. Medtronic personnel may facilitate the DMC meetings but will not have voting privileges.

Appendix E: Foreseeable Adverse Event List

The information provided in this section pertains to foreseeable adverse events that may be observed in SLATE study subjects and may assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse events information is based on AEs reported in published literature, the FDA Manufacturer and User Facility Device Experience (MAUDE) database, and Medtronic complaint handling system. Information regarding foreseeable adverse events may be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The Visualase procedure involves surgery; therefore, standard events associated with a surgical procedure may be experienced (including but not limited to anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, and the unavoidable events listed in Section 10.1 of this Clinical Investigational Plan). Additionally, the patient population eligible for inclusion in this study has an underlying disease of epilepsy; therefore, standard events associated with epilepsy may be experienced (including but not limited to seizures, injury resulting from seizures and sudden unexpected death in epilepsy). However, the focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the system under investigation.

Potential risks associated with the Visualase procedure as well as risk minimization are discussed within Section 11. Treatment required for procedure- and/or device- related adverse events that are experienced may include medication, surgical abandonment, or other surgical and medical remedies.

Observed Adverse Device Effects in Previous Clinical Studies

There have been no previous Medtronic-sponsored clinical studies evaluating use of the Visualase system for treatment of temporal lobe epilepsy.

Adverse Events in Literature & Post-market Event Reporting

The foreseeable adverse events associated with the Visualase procedure have been documented in various literature articles and in post-market event reporting. The foreseeable adverse events may include events that are possible but have not yet been reported. Adverse events associated with the Visualase System include, but are not limited to, the following:

- Anxiety
- Aphasia
- Back pain
- Blurry vision
- Brain abscess
- Bruising/ ecchymosis
- Cerebral vascular accident (CVA)
- Cerebrospinal fluid (CSF) leakage
- Death
- Deep venous thrombosis (DVT)
- Depression
- Device fragment retained in body
- Diplopia
- Edema
- Emotional lability
- Fever
- Headache
- Hematoma
- Hemianopia
- Hemiparesis
- Hemorrhage
- Herniation
- Hydrocephalus

- Infection
- Memory impairment / difficulty
- Meningitis
- Nausea
- Neurologic deficits
- Pain at incisional/access site
- Pain/discomfort/ stiffness
- Paralysis
- Persistent vegetative state
- Psychological/ psychiatric complications
- Pulmonary embolism (PE)
- Quadrantanopia
- Scalp numbness
- Scalp pain
- Seizure
- Sensory loss
- Skin abrasion or blister
- Sleep problems or insomnia
- Superficial wound infection
- Vomiting

Appendix F: Qualifying Primary Safety Endpoint Adverse Events

Adverse events will be reported per Section 10. 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 7 is a flow-chart to determine if a Study Reportable AE qualifies for inclusion in the primary safety endpoint analysis.

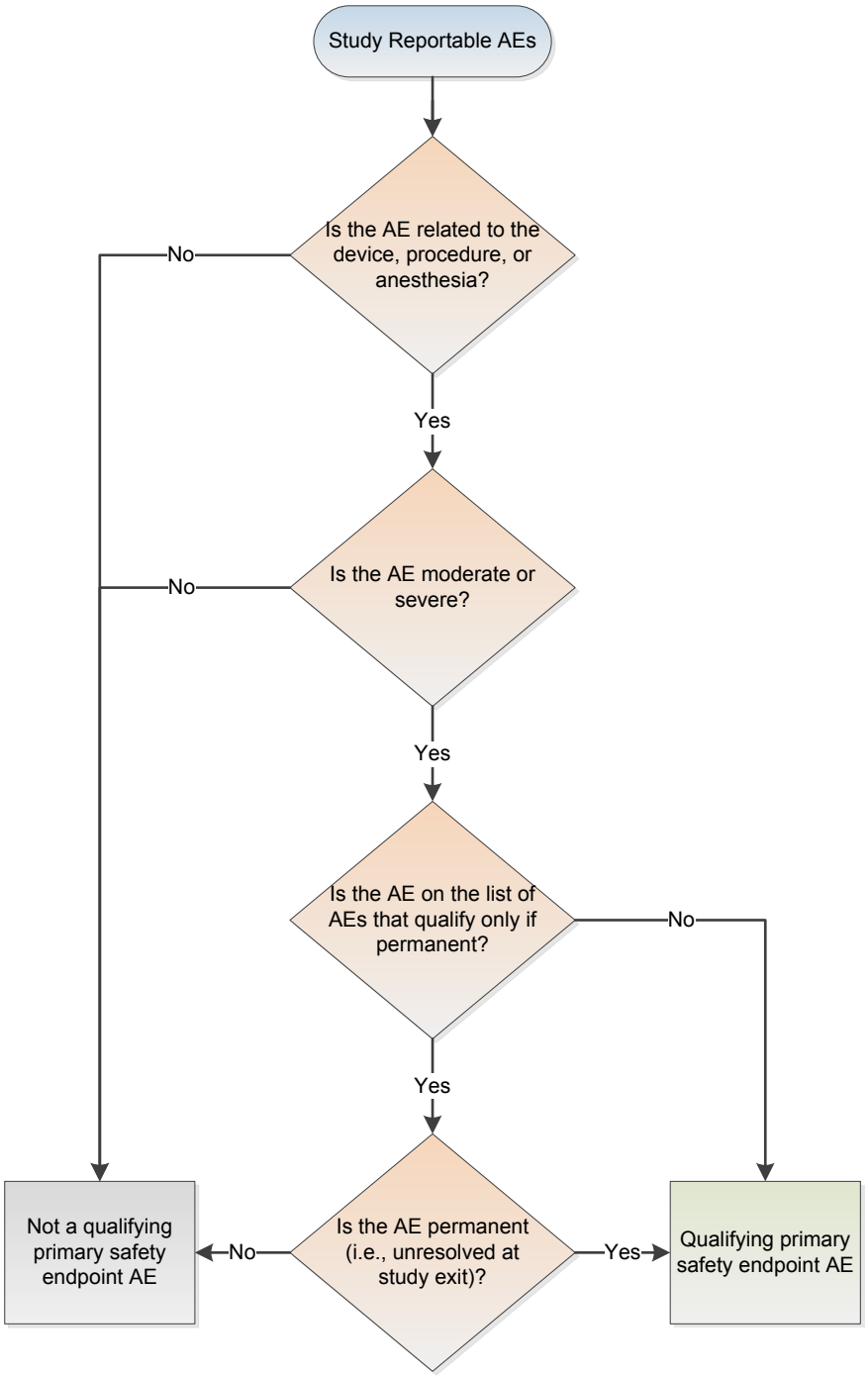


Figure 7: Qualifying Primary Safety Endpoint AE Flow Chart

Appendix G: Preliminary Publication Plan

Publications from the SLATE study will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

This study will be registered and results posted on www.clinicaltrials.gov. Medtronic, as the Sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study investigators and Medtronic personnel. Authorship will be established prior to the writing of the manuscript via a publication committee. The publication committee will develop the final publication plan as a separate document. As this study involves multiple sites, no individual publications will be allowed prior to completion of publication submission of the multicenter study except as agreed with Medtronic.

Appendix H: Other Documents

The following Clinical Investigational Plan documents will be provided separately:

- Device Labeling
- Informed Consent Form template
- List of Investigational Sites
- List of Institutional Review Boards
- SLATE Study Visualase Technique Recommendations
- SLATE Neuroimaging Manual of Operations
- SLATE Neuropsychological Manual of Operations
- SLATE Neuro-ophthalmologic Manual of Operations

Appendix I: Modifications to the Clinical Investigational Plan

Table 10 summarizes modifications made to the CIP.

Table 10: Change History

Version & Date	Applicable Sections	Change	Rationale
1.0 16 June 2016	All	Initial Release	N/A
2.0 19 July 2017	See Summary of Changes version 1.0 to 2.0	See Summary of Changes version 1.0 to 2.0	See Summary of Changes version 1.0 to 2.0
3.0 26 July 2017	See Summary of Changes version 2.0 to 3.0	See Summary of Changes version 2.0 to 3.0	See Summary of Changes version 2.0 to 3.0
4.0 09 April 2018	See Summary of Changes version 3.0 to 4.0	See Summary of Changes version 3.0 to 4.0	See Summary of Changes version 3.0 to 4.0