**F**easibility Study on **L**aser Interstitial Thermal Therapy **A**blation for the Treatment of Medically **R**efractory **E**pilepsy

**(FLARE)**

# CLINICAL STUDY PROTOCOL

**Study Number: CL10054**

Revision: B (November 6, 2017)


**Sponsor Contact:**

[redacted]

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## Principal Investigator Signature

I have read the clinical study protocol and agree to adhere to the requirements of this protocol in accordance with the ICH guidelines for good clinical practices, ISO 14155, and applicable FDA regulations.

**Printed Name:** _____

**Signature:** _____ **Date:** _____

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|---|---|
| MONTERIS MEDICAL | **F**easibility Study on **L**aser Interstitial Thermal Therapy **A**blation for the Treatment of Medically **R**efractory **E**pilepsy **(FLARE)**<br><br>**CLINICAL STUDY PROTOCOL SYNOPSIS**<br><br>**Monteris Medical Study Number: CL10054** |
| **OBJECTIVE** | The objective of this feasibility study is to characterize the performance of brain laser interstitial thermal therapy (LITT) ablation using the Monteris NeuroBlate System for the treatment of drug-refractory medial temporal lobe epilepsy in subjects who are candidates for LITT surgery. |
| **DEVICE DESCRIPTION** | The NeuroBlate System is a combination of hardware, software and disposable surgical devices used with an existing MRI scanner. The integration of these devices allows the neurosurgeon to precisely direct an MRI compatible, gas cooled, laser probe to a desired target. Once at the target, the neurosurgeon can administer LITT and monitor the thermal dose using real-time MRI thermometry data. The NeuroBlate System provides a tool to thermally ablate brain lesions of various volume, shape or location. |
| **NUMBER OF SITES AND SUBJECTS** | Subjects will be enrolled at up to 8 investigational sites in the United States to ensure that data is collected for approximately 30 subjects who undergo laser ablation. |
| **DURATION OF STUDY** | Enrollment is expected to take approximately 12 months. Each study subject will actively participate in the study for approximately 24 months. The time from the first subject's enrollment to the final subject completing the Month 24 visit is expected to be approximately 3½ years. |
| **PROTOCOL ENDPOINTS** | The primary endpoint for the study is:<br>• To characterize safety (adverse events and neuropsychological changes) of LITT for the treatment of drug-refractory medial temporal lobe epilepsy<br>The secondary endpoints for the study are:<br>• To characterize seizure outcome (based on seizure frequency and surgical outcome classifications) of study subjects treated with LITT<br>• To characterize the quality of life of study subjects treated with LITT |
| **STUDY DESIGN** | This is a multicenter, open-label, prospective designed study. Subjects who meet the eligibility criteria and sign the informed consent will undergo a Baseline visit for initial evaluations, testing and collection of demographics and medical history.<br><br>The LITT surgical procedure will be performed within 30 days of the Baseline visit. After the procedure, subjects will be seen for a brief visit prior to discharge from the hospital and again at Day 14. Subject visits will continue with office visits at Months 1, 3, 6, 9 and 12. After the Month 12 visit, subjects will have semi-annual office visits, at Months 18 and 24. Starting at Month 2, subjects will have interim monthly phone calls (the months that the subject is not seen for an office visit). Investigators will keep antiepileptic drugs stable through the Month 12 visit. |
| **STUDY ELIGIBILITY CRITERIA** | Subjects must meet all of the following **inclusion criteria**:<br>1. Diagnosis of unilateral medial temporal lobe epilepsy (MTLE) confirmed clinically and with either (1) ictal scalp recording and MRI evidence of mesial temporal sclerosis or (2) intracranial ictal onset consistent with hippocampal origin.<br>2. Subject's seizures are distinct, stereotypical events that can be reliably counted. |

| | |
|---|---|
| | 3. Based on medical record, history of 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 the Baseline visit (i.e., at least 12 qualifying seizures in the 12 months prior to the Baseline visit). *(Seizures occurring during inpatient assessment in an epilepsy monitoring unit should not be included in the average.)*<br>4. Subject is on stable antiepileptic drugs (AEDs) for 30 days prior to the Baseline visit and compliant with medication use (as reported by the subject). Stable is defined as no new or discontinued AEDs and no changes to AED total daily dose. *(Exceptions: (1) temporary changes or discontinuation of AEDs for the purposes of diagnostic or medical procedures during the 30 days preceding the Baseline visit and (2) acute, intermittent use of benzodiazepines or other rescue medications.)*<br>5. Subject has met the criteria for a medial temporal lobe resection based on the Site's standardized pre-surgical evaluation.<br>6. Subject is deemed a LITT candidate by the center's epilepsy evaluation team.<br>7. Subject is 18 years or older at the time of consent.<br>8. Subject can be reasonably expected to maintain a seizure diary alone or with the assistance of a caregiver.<br>9. If female, must be postmenopausal, surgically sterile, or, if of childbearing potential, have a serum pregnancy test with a negative result at the Baseline visit and practicing effective contraception.<br>10. Subject or legally authorized representative is able to provide appropriate consent to participate.<br>11. Subject is able to complete regular office and telephone appointments per the protocol requirements.<br>12. Subject speaks English or Spanish as a primary language. If Spanish, the Site must be able to provide a translated (IRB-approved) consent form and the Site's neuropsychologist must be willing and able to assess the subject in Spanish.<br><br>Subjects must not meet any of the following **exclusion criteria**:<br>1. Subject has a previous diagnosis of psychogenic/non-epileptic seizures in the past 2 years.<br>2. Subject has an active psychosis (unrelated to an ictal or post-ictal state), severe depression, suicide attempt or suicidal ideation within the year preceding the Baseline visit. *(Exception: Subjects with post-ictal psychiatric symptoms are not excluded.)*<br>3. Subject has been diagnosed with primary generalized seizures.<br>4. The anticipated surgery will include a brain procedure other than LITT.<br>5. Subject has undergone previous epilepsy brain surgery for seizure treatment. *(Exception: Subjects with prior diagnostic electrode placement are not excluded.)*<br>6. Within the 5 years prior to the Baseline visit, the subject has had an MRI showing evidence of a neurological condition likely to progress. Conditions leading to exclusion include active encephalitis, active meningitis, abscess, or brain tumor.<br>7. Subject has a vascular malformation of the brain (e.g., arteriovenous malformation, cavernous malformation).<br>8. Subject has been diagnosed with a progressive or degenerative neurological disorder (e.g., multiple sclerosis).<br>9. Subject has a significant medical condition that is likely to worsen during the study period.<br>10. Subject has an IQ less than 70 based on the Baseline visit testing. If Spanish-speaking, a score lower than the 5th percentile on Raven's Standard Progressive Matrices is exclusionary.<br>11. Subject has malignancy or history of malignancy within 5 years prior to the Baseline visit. *(Exception: Subjects with skin cancers other than melanoma are not excluded.)*<br>12. Subject has physical dimensions that cannot be accommodated in the MRI scanner. |

| | |
|---|---|
| | 13. Subject has a MRI-incompatible implanted electronic device or any metallic prosthesis or implant for which brain MRI is contraindicated.<br>14. Subject has risk factors for intraoperative or postoperative bleeding, as determined by the investigator.<br>15. Subject has ongoing or recent alcohol or substance abuse as determined by the investigator.<br>16. Subject is participating in another investigational device, drug, or surgical study. |
| **CEC AND DSMB** | A Clinical Event Committee will review and adjudicate reported adverse events; a Data Safety Monitoring Board will review summarized safety data. |
| **MRI CORE LAB** | An MRI core laboratory will be used to provide an unbiased assessment of MRI measures, including brain tissue response to LITT and volume of the lesion. |

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# 1 ABBREVIATIONS

The following is a list of abbreviations used in the body of this document. Abbreviations solely used in tables (e.g., table headers) are described in the table footer and are not included below.

| | |
|---|---|
| ADE | adverse device effect |
| AE | adverse event |
| AED | antiepileptic drug |
| AVLT | Auditory Verbal Learning Test |
| BVMT-R | Brief Visual Memory Test – Revised |
| BNT-60 | Boston Naming Test – 60 item version |
| CE | "Conformité Européene" (European Conformity) |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| DSMB | Data Safety and Monitoring Board |
| COWAT | Controlled Oral Word Association Test |
| CRF | case report form |
| CRO | contract research organization |
| ICF | informed consent form |
| IFU | Instructions for Use |
| IQ | intelligence quotient |
| ILAE | International League Against Epilepsy |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| LDP | laser delivery probe |
| LITT | laser interstitial thermal therapy |
| MRI | magnetic resonance imaging |
| MTLE | mesial temporal lobe epilepsy |
| NAV | not available |
| NBS | NeuroBlate® System |
| NINDS | National Institute of Neurological Disorders and Stroke |
| nm | nanometer |
| QOLIE-31 | Quality of Life in Epilepsy – 31 item version |
| PI | principal investigator |
| PS-BNT | Ponton-Satz Boston Naming Test |
| RAVLT | Rey Auditory Verbal Learning Test |
| SADE | serious adverse device effect |
| SAE | serious adverse event |
| SFP | SideFire Probe |
| SOP | standard operating procedures |
| SPM | Standard Progressive Matrices |
| UADE | unanticipated adverse device effect |
| USADE | unanticipated serious adverse device effect |
| VAS | visual analog scale |
| WAIS-IV | Wechsler Adult Intelligence Scale-IV |
| WMS-IV | Wechsler Memory Scale-IV |

# 2 INTRODUCTION

Since its introduction to neurosurgery over 25 years ago, laser ablation had been largely confined to the management of unresectable tumors. The application of this technology for management of medically refractory epilepsy is being explored as a treatment option.[1, 2] Laser interstitial thermal therapy (LITT) is a minimally invasive option to open surgical intervention that necrotizes abnormal intracranial tissues. LITT's use in neurosurgical procedures was historically limited by early technical difficulties related to the monitoring and control of thermal distribution. The development of magnetic resonance thermography and its application to LITT provides real-time thermal imaging and feedback control during laser energy delivery, resulting in precise and accurate delivery of tissue hyperthermia. Improvements in laser probe design, surgical stereotactic targeting hardware and computer monitoring software has accelerated clinical utilization of LITT as a refractory epilepsy treatment alternative for eligible patients although clinical outcome data is limited. [1]

The NeuroBlate® System (NBS) is a robotic laser thermotherapy tool manufactured by Monteris Medical (Sponsor). The NBS combines magnetic resonance imaging (MRI) and software-based visualization allowing the surgeon to necrotize targeted tissues at the surface of or deep inside the brain through a pencil-sized hole in the skull. An MRI compatible robotic probe driver helps the surgeon precisely guide the laser probe to the targeted tissue and apply heat to it in controlled amounts under guidance of real-time MR thermography, until the tissue is destroyed.

The Sponsor designed this multicenter, open-label, prospective feasibility study to characterize the performance of LITT ablation using the Monteris NBS for the treatment of drug refractory medial temporal lobe epilepsy in subjects who are candidates for surgical resection.

# 3 TREATMENT DESCRIPTION

## 3.1 Device and Components

The NBS is a combination of hardware, software and disposable surgical devices used with an existing MRI scanner. The integration of these devices allows the neurosurgeon to precisely direct an MRI compatible, gas cooled, laser probe to a desired target. Once at the target, the neurosurgeon can administer LITT and monitor the thermal dose using real-time MRI thermometry data. The NBS provides a tool to thermally ablate brain lesions of various volume, shape or location.

The NBS hardware and disposable accessories are outlined in Table 1.1 of the Instructions for Use (IFU). Optional disposable and reusable devices available from Monteris are outlined in Table 1.2 of the IFU. Key components are described below:

*Laser Delivery Probes (LDP)*: The NBS family of LDPs are single-use (disposable) patient interface components used to deliver laser interstitial thermal therapy. They are composed of MRI-compatible

[1] Missios S, Bekelis K, Barnett GH. Renaissance of laser interstitial thermal ablation. *Neurosurg Focus*. 2015;38(3):E13.

[2] Hawasli AH, Bandt SK, Hogan RE, Werner N, Leuthardt EC. Laser ablation as treatment strategy for medically refractory dominant insular epilepsy: therapeutic and functional considerations. *Stereotact Funct Neurosurg.* 2014;92(6):397-404.

materials allowing for gas cooling during simultaneous laser application and thermal imaging. The LDPs are available in multiple lengths and configurations. The appropriate length is determined during clinical use by the NBS M·Vision software. The appropriate probe configuration and diameter is determined by the physician depending on the clinical need.

*SideFire™ Directional Laser Probe (SFP):*

The SideFire™ Directional Laser Probe tip (Figure 1) emit controlled laser energy in a uniform direction at approximately 78 degrees from the long axis of the SFP.

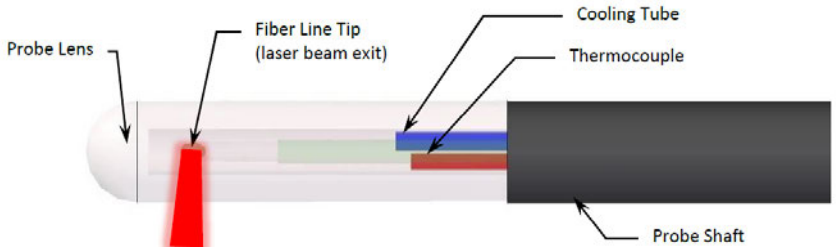


**Figure 1: SideFire™ Directional Laser Probe Tip**

*FullFire™ and FullFire™ Select Diffusing Tip Laser Probe*

The FullFire™ and smaller diameter FullFire™ Select Diffusing Tip Laser Probe are comprised of the same components and mechanical interfaces as the SideFire™ Directional Laser Probe. The FullFire™ and FullFire™ Select Probe is differentiated by laser energy dispersion in all directions/dimensions (3-dimension, see representative red arrows in Figure 2).

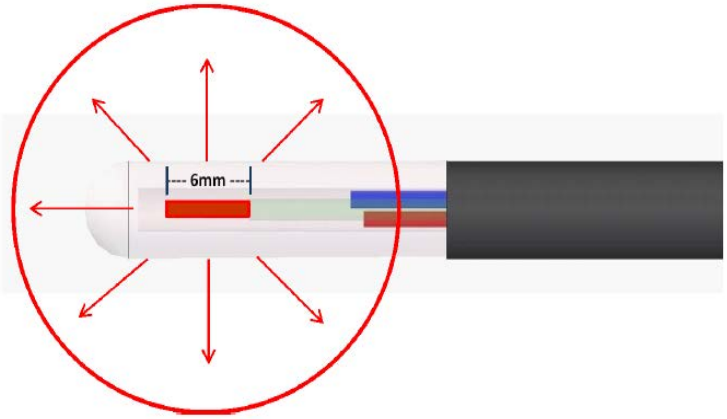


**Figure 2: FullFire™ Diffusing Laser Probe Tip**

### 3.2 Indications for Use

The NeuroBlate System is commercially available. The indication for use is as follows:

> *The Monteris Medical NeuroBlate System is indicated for use to ablate, necrotize, or coagulate intracranial soft tissue, including brain structures, through interstitial irradiation or thermal therapy in medicine and surgery in the discipline of neurosurgery with 1064 nm lasers.*
>
> *The Monteris Medical NeuroBlate System is intended for planning and monitoring thermal therapies under MRI visualization. It provides MRI-based trajectory planning assistance for the stereotaxic placement of MRI compatible (conditional) NeuroBlate Laser Delivery Probes. It also provides real-time thermographic analysis of selected MRI images.*
>
> *When interpreted by a trained physician, this System provides information that may be useful in the determination or assessment of thermal therapy. Patient management decisions should not be made solely on the basis of the NeuroBlate System analysis.*

## 4 OBJECTIVE

The objective of this feasibility study is to characterize the performance of brain LITT ablation using the Monteris NeuroBlate System for the treatment of drug-refractory medial temporal lobe epilepsy in subjects who are candidates for LITT surgery.

## 5 ENDPOINTS

The primary endpoint for the study is:

- To characterize safety (adverse events and neuropsychological changes) of LITT for the treatment of drug-refractory medial temporal lobe epilepsy

The secondary endpoints for the study are:

- To characterize seizure outcome (based on seizure frequency and surgical outcome classifications) of study subjects treated with LITT
- To characterize the quality of life of study subjects treated with LITT

## 6 STUDY DESIGN

The study is a multicenter, open-label, prospective design study.

### 6.1 Number of Sites and Subjects

Subjects will be enrolled at up to 8 investigational sites (Sites) in the United States to ensure that data is collected from approximately 30 subjects who undergo laser ablation.

## 6.2 Study Duration

Enrollment is expected to take approximately 12 months. Each study subject will actively participate in the study for approximately 24 months. The time from the first subject's enrollment to the final subject completing the Month 24 visit is expected to be approximately 3½ years.

## 6.3 Study Eligibility Criteria (Inclusion/Exclusion)

Study eligibility criteria (inclusion and exclusion) are listed below.

### *6.3.1 Study Inclusion Criteria*

Subjects must meet all of the following inclusion criteria:

1. Diagnosis of unilateral medial temporal lobe epilepsy (MTLE) confirmed clinically and with either (1) ictal scalp recording and MRI evidence of mesial temporal sclerosis or (2) intracranial ictal onset consistent with hippocampal origin
2. Subject's seizures are distinct, stereotypical events that can be reliably counted.
3. Based on medical record, history of 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 the Baseline visit (i.e., at least 12 qualifying seizures in the 12 months prior to the Baseline visit). *(Seizures occurring during inpatient assessment in an epilepsy monitoring unit should not be included in the average)*.
4. Subject is on stable antiepileptic drugs (AEDs) for 30 days prior to the Baseline visit and compliant with medication use (as reported by the subject). Stable is defined as no new or discontinued AEDs and no changes to AED total daily dose. *(Exception: (1) temporary changes or discontinuation of AEDs for the purposes of diagnostic or medical procedures during the 30 days preceding the Baseline visit and (2)* acute, intermittent use of benzodiazepines or other rescue medications*.)*
5. Subject has met the criteria for a medial temporal lobe resection based on the Site's standardized pre-surgical evaluation.
6. Subject is deemed a LITT candidate by the center's epilepsy evaluation team.
7. Subject is 18 years or older at the time of consent.
8. Subject can be reasonably expected to maintain a seizure diary alone or with the assistance of a caregiver.
9. If female, must be postmenopausal, surgically sterile, or, if of childbearing potential, have a serum pregnancy test with a negative result at the Baseline visit and practicing effective contraception.[3]
10. Subject or legally authorized representative is able to provide appropriate consent to participate.
11. Subject is able to complete regular office and telephone appointments per the protocol requirements.
12. Subject speaks English or Spanish as a primary language. If Spanish, the Site must be able to provide a translated (IRB-approved) consent form and the Site's neuropsychologist must be willing and able to assess the subject in Spanish.

[3] Inclusion criteria may need to be evaluated after obtaining informed consent, if it not part of the Site's standard of care for epilepsy management and/or surgery evaluation.

### *6.3.2 Study Exclusion Criteria*

The subject must not meet any of the following exclusion criteria:

1. Subject has a previous diagnosis of psychogenic/non-epileptic seizures in the past 2 years.
2. Subject has an active psychosis (unrelated to an ictal or post-ictal state), severe depression, suicide attempt or suicidal ideation within the year preceding the Baseline visit. *(Exception: Subjects with post-ictal psychiatric symptoms are not excluded.)*
3. Subject has been diagnosed with primary generalized seizures.
4. The anticipated surgery will include a brain procedure other than LITT.
5. Subject has undergone previous epilepsy brain surgery for seizure treatment. *(Exception: Subjects with prior diagnostic electrode placement are not excluded.)*
6. Within the 5 years prior to the Baseline visit, the subject has had an MRI showing evidence of a neurological condition likely to progress. Conditions leading to exclusion include active encephalitis, active meningitis, abscess, or brain tumor.
7. Subject has a vascular malformation of the brain (e.g., arteriovenous malformation, cavernous malformation).
8. Subject has been diagnosed with a progressive or degenerative neurological disorder (e.g., multiple sclerosis).
9. Subject has a significant medical condition that is likely to worsen during the study period.
10. Subject has an IQ less than 70 based on the Baseline visit testing. If Spanish-speaking, a score lower than the 5th percentile on Raven's Standard Progressive Matrices is exclusionary.* [4]
11. Subject has malignancy or history of malignancy within 5 years prior to the Baseline visit. (Exception: Subjects with skin cancers other than melanoma are not excluded.)
12. Subject has physical dimensions that cannot be accommodated in the MRI scanner.
13. Subject has a MRI-incompatible implanted electronic device or any metallic prosthesis or implant for which brain MRI is contraindicated.
14. Subject has risk factors for intraoperative or postoperative bleeding, as determined by the investigator.
15. Subject has ongoing or recent alcohol or substance abuse as determined by the investigator.
16. Subject is participating in another investigational device, drug, or surgical study.

# 7 STUDY METHODOLOGY

## 7.1 Trial Summary

Subjects who meet the study eligibility criteria and sign the informed consent form (ICF) will undergo a Baseline visit for initial evaluations, testing and collection of demographics and medical history.

The LITT surgical procedure will be performed within 30 days of the Baseline visit. After the procedure, subjects will be seen for a brief visit prior to discharge from the hospital and again at the Day 14 visit. Subject visits will continue with office visits at Months 1, 3, 6, 9 and 12. After the Month 12 visit, subjects will have semi-annual office visits, at Months 18 and 24. Starting at Month 2, subjects will have

[4] Exclusion criteria may need to be evaluated after obtaining informed consent, if it not part of the Site's standard of care for epilepsy management and/or surgery evaluation.

interim monthly phone calls (the months that the subject is not seen for an office visit). Investigators will keep AEDs stable through the Month 12 visit.

The study design is outlined in Figure 3.

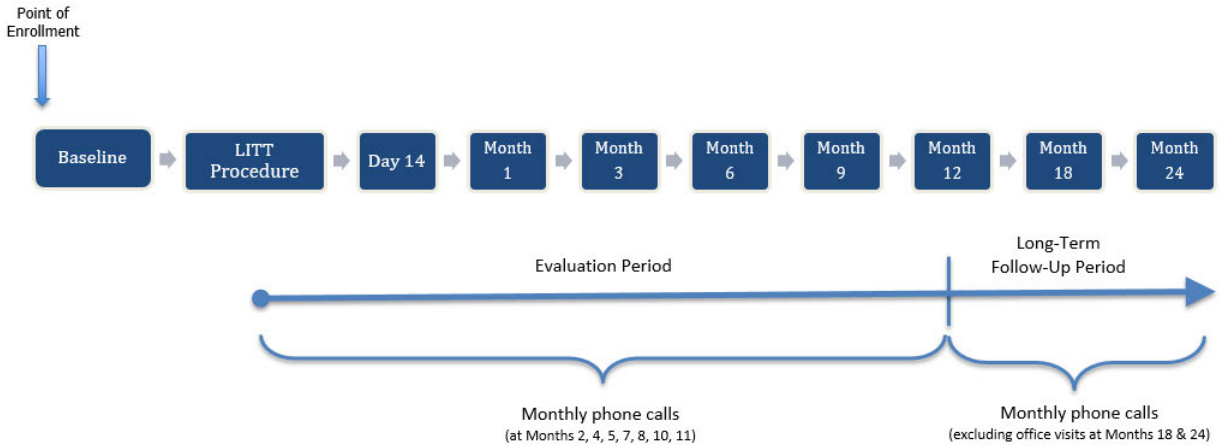


**Figure 3: Study Design Schema**

## 7.2 Screening

Screening is defined as the process of reviewing a patient's medical records against the study eligibility (inclusion and exclusion) criteria to determine if the patient is eligible to enroll in the study. It is expected that the medical records will contain adequate information to determine if a patient meets most of these criteria. If a patient meets most of the eligibility criteria, they can be consented for the study. If a patient is not consented they are considered a screening failure. Screening failures will be tracked on a Screening and Enrollment Log.

## 7.3 Informed Consent

The investigator or authorized delegate will explain the nature of the planned treatment and objectives of the study to a patient (or patient's legally authorized representative). The investigator or authorized delegate will allow adequate time for the patient or legal representative to read and review the consent form and to ask questions.

The patient (or the patient's legally authorized representative) and the investigator (or authorized delegate) will sign and date the Institutional Review Board (IRB)-approved ICF. The original signed ICF form will be retained in the subject's study records. A copy of the signed ICF will be provided to the subject (or legal representative) and a copy placed in the subject's medical records.

The investigator or authorized delegate must document in the subject's medical records that the subject was consented and the date on which the consent was obtained, and that a copy of the signed ICF was given to the subject.

## 7.4 Point of Enrollment and Numbering of Study Subjects

A patient will be considered enrolled as a study subject when they have met all study eligibility criteria and have signed the informed consent form (or their legally authorized representative has signed). The study database will assign the subject number. At the time of subject enrollment, the investigator or other study team member will notify the contract research organization (CRO) via fax or email.

## 7.5 Schedule of Visits and Testing Requirements

Table 1 and Table 2 outline the visits, visit windows, and testing requirements at each evaluation time point.

**Table 1: Visits and Testing Requirements and Data Collection Summary (Baseline through Month 12)**

| | Baseline | | | | | | Post-Procedure | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | LITT Proc. | DC | Day 14 | Mo. 1 | Mo. 2 | Mo. 3 | Mo. 4 | Mo. 5 | Mo. 6 | Mo. 7 | Mo. 8 | Mo. 9 | Mo. 10 | Mo. 11 | Mo. 12 |
| *Visit Window* | *Within 7 days of enrollment* | | | | *Within 30 days of Baseline[1]* | *Day of DC* | *±4 days* | *±4 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* | *±7 days* |
| *Visit Type* | | | | | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | √ | | | | | | | | | | | | | | | | | | |
| Informed consent | √ | | | | | | | | | | | | | | | | | | |
| Demographics | √ | | | | | | | | | | | | | | | | | | |
| Medical, surgical & epilepsy history | √ | | | | | | | | | | | | | | | | | | |
| QOLIE-31 | √ | | | | | | | | | | | | √ | | | | | | √ |
| Medication review (epilepsy and non-epilepsy) | √ | | | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Physical exam | √ | | | | | √ | | √ | | | | | √ | | | | | | √ |
| Neurological exam | √ | | | | | √ | | √ | | √ | | | √ | | | √ | | | √ |
| Formal visual field testing | √ | | | | | | | | | | | | √ | | | | | | |
| Serum pregnancy test (if female of child-bearing potential) | √ | | | | | | | | | | | | | | | | | | |
| Neuropsychological testing [2] | √[3] | | | | | | | | | √ | | | √ | | | | | | √ |
| Functional assessment | √ | | | | | | √ | √ | | √ | | | √ | | | √ | | | √ |
| Seizure classification assessment | I | | | | | | | | | U | | | U | | | | | | U |
| Seizure diary | T | | | | | T/D | C/D | C/D | C | C/D | C | C | C/D | C | C | C/D | C | C | C/D |
| Adverse event monitoring | | | | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Treatment criteria | | | | | | | | | | | | | | | | | | | |
| LITT treatment | | | | | √ | | | | | | | | | | | | | | |
| MRI | | | | | √ | √[4] | | | | | | | √ | | | | | | |
| Surgical pain VAS | | | | | | √ | √ | | | | | | | | | | | | |
| Surgical outcome classifications[5] | | | | | | | | | | √ | | | √ | | | √ | | | √ |
| Subject satisfaction | | | | | | | | | | | | | √ | | | | | | √ |

Abbreviations: C, collect; D, dispense; DC, discharge; I, initial; LITT, laser interstitial thermal therapy; Mo., month; MRI, magnetic resonance imaging; proc., procedure; QOLIE-31, Quality of Life in Epilepsy - 31; T, training; U, update; VAS, visual analog scale.

[1] Surgery may be performed >30 days after the Baseline Visit if needed to accommodate neuropsychological test scheduling.

[2] See Appendix C for details of the neuropsychological testing at each visit. These can be performed on a separate day than the Baseline visit.

[3] Prior neuropsychological testing may be used for Baseline if the testing was conducted within 6 months prior to the Baseline visit and there were no significant changes to the subject's AEDs or changes to the subject's clinical condition that may affect cognitive function.

[4] The MRI performed at the end of the LITT procedure may be used as the Discharge Visit MRI.

[5] See Appendix D for details about the Engel and ILAE surgical outcome classifications.

**Table 2: Visits and Testing Requirements and Data Collection Summary (Month 12 through Month 24)**

| *Visit Window* | Months 13, 14, 15, 16, & 17 *± 7 days* | Month 18 *± 14 days* | Months 19, 20, 21, 22, & 23 *± 7 days* | Month 24 *± 14 days* | Early Withdrawal |
|---|---|---|---|---|---|
| *Visit Type* | ☎ | 🏠 | ☎ | 🏠 | |
| QOLIE-31 | | √ | | √ | √ |
| Medication review (epilepsy and non-epilepsy) | √ | √ | √ | √ | |
| Neurological exam | | √ | | √ | √ |
| Functional assessment | | √ | | √ | √ |
| Seizure diary | C/D | C/D | C/D | C | √ |
| Adverse event monitoring | √ | √ | √ | √ | √ |
| Surgical outcome classifications[1] | | √ | | √ | √ |
| Subject satisfaction | | √ | | √ | √ |
| Neuropsychological testing[2] | | | | | √ |

Abbreviations: C; collect; D, dispense; QOLIE-31, Quality of Life in Epilepsy - 31; U, update.
[1] See Appendix D for details about the Engel and ILAE surgical outcome classifications.

## 7.6 Procedures and Subject Assessments

### *7.6.1 Baseline Visit*

Prior to consenting patients for the study, Site personnel will evaluate potential candidates by reviewing the patient medical records against the study eligibility criteria. It is expected that the medical records will contain adequate information to determine if the patient meets these criteria. Potential patients will be asked to complete the informed consent process.

The following evaluations and assessments will be performed at this visit:

- Demographics
- Medical, surgical and epilepsy history
  - Epilepsy history will include collection of 12 months of retrospective seizure frequency data; data from the 3 months prior to the Baseline visit will be used for eligibility determination. See Appendix B for more details.
- Quality of Life in Epilepsy - 31 (QOLIE-31). It is preferred that the subject completes the questionnaire prior to any other baseline tests.
- Medication review, including collection of 12 months of retrospective epilepsy medication data (as available) to qualitatively assess medication stability prior to the NeuroBlate procedure. See Appendix A for more details.
- Physical exam
- Neurological exam
- Visual field testing (automated perimetry)
- Serum pregnancy test (if female and of childbearing potential)
- Neuropsychological testing (see Appendix C).
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure classification assessment
- Seizure diary training

### *7.6.2 LITT Procedure*

An MRI will be performed prior to surgery to determine trajectory and frame/arc settings. The LITT procedure will be performed per the IFU. Adverse events that occur during the procedure will be collected.

Postoperatively, the subject should be managed per the institution's standard of care for subjects receiving LITT. This includes monitoring of the subject's neurological status as it relates to possible intraoperative or postoperative adverse events (including intracranial hemorrhage).

Subjects experiencing a failed LITT treatment attempt (stopping the procedure prior to thermal delivery) will be followed for 1 month post-procedure for adverse events.

### *7.6.3 Discharge Visit*

Prior to hospital discharge the following evaluations and assessments will be performed:

- Medication review (see Appendix A)
- Physical exam
- Neurological exam
- Adverse event monitoring
- MRI (the MRI performed at the end of the LITT procedure can be used as the Discharge Visit MRI).
- Surgical pain visual analog scale (VAS)
- Seizure diary training refresher and dispensing (see Appendix B)

### *7.6.4 Day 14 Visit*

The following evaluations and assessments will be performed at this visit:

- Medication review (see Appendix A)
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure diary collection and dispensing (see Appendix B)
- Adverse event monitoring
- Surgical pain VAS

### *7.6.5 Month 1 Visit*

The following evaluations and assessments will be performed at this visit:

- Medication review (see Appendix A)
- Physical exam
- Neurological exam
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure diary collection and dispensing (see Appendix B)
- Adverse event monitoring

### *7.6.6 Month 2 Telephone Call*

The following assessments will be completed during this call:

- Medication review (see Appendix A)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

### *7.6.7 Month 3 Visit*

The following evaluations and assessments will be performed at this visit:

- Medication review (see Appendix A)
- Neurological exam
- Neuropsychological testing (see Appendix C).
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure classification update assessment
- Seizure diary collection and dispensing (see Appendix B)
- Adverse event monitoring
- Surgical outcome classifications (Engel and ILAE, see Appendix D)

### *7.6.8 Month 4 Telephone Call*

The following assessments will be completed during this call:

- Medication review (see Appendix A)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

### *7.6.9 Month 5 Telephone Call*

The following assessments will be completed during this call:

- Medication review (see Appendix A)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

### *7.6.10 Month 6 Visit*

The following evaluations and assessments will be performed at this visit:

- QOLIE-31. It is preferred that the subject completes the questionnaire prior to any other tests.
- Medication review (see Appendix A)
- Physical exam
- Neurological exam
- Visual field testing (automated perimetry)
- Neuropsychological testing (see Appendix C).
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure classification update assessment

- Seizure diary collection and dispensing (see Appendix B)
- Adverse event monitoring
- MRI
- Surgical outcome classifications (Engel and ILAE, see Appendix D)
- Subject satisfaction

### *7.6.11 Month 7 Telephone Call*

The following assessments will be completed during this call:

- Medication review (see Appendix A)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

### *7.6.12 Month 8 Telephone Call*

The following assessments will be completed during this call:

- Medication review (see Appendix A)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

### *7.6.13 Month 9 Visit*

The following evaluations and assessments will be performed at this visit:

- Medication review (see Appendix A)
- Neurological exam
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure diary collection and dispensing (see Appendix B)
- Adverse event monitoring
- Surgical outcome classifications (Engel and ILAE, see Appendix D)

### *7.6.14 Month 10 Telephone Call*

The following assessments will be completed during this call:

- Medication review (see Appendix A)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

### *7.6.15 Month 11 Telephone Call*

The following assessments will be completed during this call:

- Medication review (see Appendix A)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

### *7.6.16 Month 12 Visit*

The following evaluations and assessments will be performed at this visit:

- QOLIE-31. It is preferred that the subject completes the questionnaire prior to any other tests.
- Medication review (see Appendix A)
- Physical exam
- Neurological exam
- Neuropsychological testing (see Appendix C)
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure classification update assessment
- Seizure diary collection and dispensing (see Appendix B)
- Adverse event monitoring
- Surgical outcome classifications (Engel and ILAE, see Appendix D)
- Subject satisfaction

### *7.6.17 Telephone Calls (Months 13-17, 19-23)*

During these phone calls the following assessments will be completed:

- Medication review (see Appendix A)
- Seizure diary collection and dispensing (see Appendix B)
- Adverse event monitoring

### *7.6.18 Month 18 Visit*

The following evaluations and assessments will be performed at this visit:

- QOLIE-31. It is preferred that the subject completes the questionnaire prior to any other tests.
- Medication review (see Appendix A)
- Neurological exam
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure diary collection and dispensing (see Appendix B)
- Surgical outcome classifications (Engel and ILAE, see Appendix D)
- Adverse event monitoring
- Subject satisfaction

### *7.6.19 Month 24 Visit*

The following evaluations and assessments will be performed at this visit:

- QOLIE-31. It is preferred that the subject complete the questionnaire prior to any other tests.
- Medication review (see Appendix A)
- Neurological exam
- Functional assessment (including employment status, education, living arrangements, driving status)
- Seizure diary collection (see Appendix B)
- Adverse event monitoring

- Surgical outcome classifications (Engel and ILAE, see Appendix D)
- Subject satisfaction

#### *7.6.20 Unscheduled Visit*

Evaluations or assessments completed during an unscheduled visit will be recorded on the applicable CRFs.

### 7.7 Additional LITT Procedure(s)

If a subject undergoes an additional LITT MTLE procedure for persistent seizures, the following evaluations and CRFs will be completed:

- *Neuropsychological Testing* CRF (testing must be completed prior to the procedure)
- Evaluation CRF (for an unscheduled (Discharge) visit )
- LITT Procedure CRF

### 7.8 Early Withdrawal/Premature Discontinuation of Subjects

Subjects may be withdrawn early from the study for a number of reasons, including:

- Subjects experiencing a failed LITT treatment attempt. A failed LITT treatment attempt is defined as stopping the procedure prior to thermal delivery. (Subjects that experience a failed treatment attempt will be followed for 1 month post-procedure for related adverse events.)
- Subject death
- Subject lost to follow-up
- Subject request for withdrawal
- Adverse events
- Investigator decision (other than an adverse event)

If a study subject is discontinued from the study early, a Study Completion CRF must be completed describing the reason for early discontinuation. The investigator should make all attempts to conduct an Early Withdrawal visit at the time of withdrawal from the study. If a subject has withdrawn consent for the study or is lost to follow-up, the completion of this visit is not imperative. In situations where study withdrawal is due to an adverse event, subjects will be followed until resolution of the adverse event or determination that the subject's condition is stable.

At the Early Withdrawal visit, the subject will undergo the following evaluations:

- QOLIE-31. It is preferred that the subject completes the questionnaire prior to any other tests.
- Neurological exam (cranial nerves (including confrontational visual field testing), motor, coordination, reflexes, gait, sensation)
- Neuropsychological testing
- Adverse event monitoring
- Subject satisfaction
- Functional assessment (including employment status, education, living arrangements, driving status)
- Surgical outcome classifications (Engel and ILAE, see Appendix D)

If a subject chooses to withdraw from the study and also withdraws consent for disclosure of future information, no further evaluation(s) should be performed and no additional data will be collected. The Sponsor may retain and continue to use any data collected prior to the withdrawal of consent.

### 7.9 Handling of Lost-to-Follow-up Subjects

Every attempt must be made to have all subjects complete the follow-up visit schedule. A subject will be considered lost-to-follow-up when all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three attempts to make contact via telephone and if contact via phone is not successful, a certified letter from the principal investigator (PI) or authorized delegate must be sent to the subject's last known address. Both telephone and letter contact efforts to obtain follow up must be documented in the subject's medical records and on the Study Completion case report form (CRFs).

## 8 MEASURES TO AVOID AND MINIMIZE BIAS

The study has several measures that have been implemented to avoid and minimize bias, namely, establishment of an independent Data Safety Monitoring Board (DSMB), Clinical Events Committee (CEC), and the use of an MRI core laboratory.

### 8.1 Data Safety Monitoring Board

The DSMB will be a group comprised of individuals who are independent of the Sites. The board will be comprised of representatives from multiple disciplines including but not limited to epilepsy, neurosurgery, and biostatistics/epidemiology.

The board will establish a DSMB charter which will contain data monitoring criteria for the study, including frequency of meetings, review of aggregate data, and stopping rules if safety concerns arise from their review of the study data.

### 8.2 Clinical Events Committee

The CEC will be a group comprised of individuals who are independent of the Sites. The board will be comprised of representatives from multiple disciplines including but not limited to epilepsy and neurosurgery.

The Committee will establish adjudication guidelines governing their periodic review and adjudication of adverse events to assure appropriate and consistent classification.

### 8.3 MRI Core Laboratory

An MRI core laboratory will be used to provide an unbiased assessment of MRI measures, including brain tissue response to LITT and volume of the lesion.

A core laboratory charter will outline image acquisition and processing, and other functions of the core laboratory.

# 9 ADVERSE EVENTS

## 9.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs whether or not related to the investigational medical device. This includes events related to the medical device and events related to the procedures involved.

Disease signs and symptoms that existed prior to study participation are not considered AEs unless the condition worsens in intensity or frequency during the study.

Collection of AEs will start on the day of the procedure and will be assessed and reported throughout the study. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to the Sponsor or CRO. All reported AEs will be documented on the CRF. All AEs will be followed until resolution or PI determination that the subject's condition is stable.

The following are not considered adverse events for this study:

- Any normal expected postoperative complaints or symptoms unless the event involves a clinically significant change in severity or duration of symptoms, or requires clinical intervention that is different from ordinary postoperative care. Expected postoperative complaints and findings include, but are not limited to: headache, edema (on MRI), nausea and vomiting, and postoperative pain.
- Any condition that is recorded as pre-existing on the Baseline CRF, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
- Planned hospitalization for a pre-existing condition or a procedure required by the protocol, without serious deterioration in health.

Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of the study device.

This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment or operation, or any malfunction of the medical device. This definition also includes any event from an error in usage or from intentional misuse of the medical device.

Serious Adverse Event

A serious adverse event (SAE) is an AE that:

- Led to death;
- Led to serious deterioration in the health of the subject, that resulted in:
  - a life-threatening illness or injury, or

  - a permanent impairment of a body structure or a body function, or
  - hospital admission (>24 hours) or prolongation of an existing hospitalization, or
  - medical or surgical intervention to prevent permanent life-threatening illness or injury, or permanent impairment to a body structure or a body function;
- Led to fetal distress, fetal death or a congenital anomaly or birth defect

**Note**: An adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an AE or an SAE.

Serious Adverse Device Effect

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Anticipated Serious Adverse Device Effect

An anticipated serious adverse device effect is an effect which by its nature, incidence, severity or outcome, has been identified in the risk analysis report.

Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is a serious adverse effect, which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report, protocol or application (including a supplementary plan or application). USADEs are also commonly called unanticipated adverse device effects (UADE), as defined in 21 CFR 812.3 (s).

Device Malfunction

A device malfunction is defined as a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or protocol.

AE Severity

The severity of an adverse event is a qualitative judgment of the degree of intensity, as determined by the PI. The severity of the adverse event should be evaluated according to the following scale:

- **Mild:** Does not interfere in a significant manner with the subject's normal functioning level.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health.
- **Severe:** Produces significant impairment of function or incapacitation and is a hazard to the subject's health.

The assessment of severity should be made independent of the relationship to the device and therapy or the seriousness of the event.

AE Relationship

The investigator will assess the relationship of the adverse event to the device treatment or procedure as follows:

- **Definite** – The adverse event follows a strong temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure. This can include an adverse event that occurs after the study procedure.
- **Probable** – The adverse event follows a reasonable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, and the possibilities of other factors, such as underlying and concomitant illness, concomitant medications, or concurrent treatment can be excluded.
- **Possible** – The adverse event follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure and the possibility of device treatment or procedure involvement cannot be excluded. However, other factors such as underlying or concomitant illness, concomitant medications, or concurrent treatment are presumable.
- **Unlikely** – The adverse event has an improbable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying or concomitant illness, concomitant medications, or concurrent treatment.
- **Not Related** – The adverse event has no temporal sequence to the LITT procedure, NeuroBlate System or any user handling, or it can be explained by other factors, including underlying disease or concomitant illness, concomitant medication, or concurrent treatment.

If the event was assessed by the investigator as *unlikely* or *not-related* to the study device treatment or procedure, one of the following alternate causations will be recorded:

- **New illness/injury**: Event is a new illness or injury that is not part of the subject's baseline medical history.
- **Pre-existing condition/disease**: Event is a worsening or exacerbation of a pre-existing condition/disease (such as epilepsy or other items listed in the baseline medical history).
- **Anesthesia**: Event is related to anesthesia.
- **Epilepsy medication**: Event has a strong temporal relationship to an epilepsy medication.
- **Non-epilepsy medication**: Event has a strong temporal relationship to a non-epilepsy medication.
- **Unknown**: Event relationship is not known or unsure.

## 9.2 Reporting

Subjects will be carefully monitored during the study for possible AEs. Any AE that occurs between the day of the procedure and the end of study participation will be fully evaluated by the investigator.

The Site will report all AEs (anticipated and unanticipated) on an *Adverse Event* CRF. Copies of source documentation which contain significant information related to the event such as progress notes, consultations, nurse's notes, operative reports and subject summaries, etc. may be requested by the

Sponsor or CRO as needed for evaluation of SAEs and ADEs. Copies of such documentation will be obtained from the investigator (or authorized delegate), de-identified as to the subject's identity, and provided to the Sponsor or CRO.

Device malfunctions will be recorded on the LITT Procedure and Discharge CRF. If a device malfunction results in the subject experiencing any untoward medical occurrence, unintended disease or injury, or untoward clinical signs, it will also be reported as an adverse event on an *Adverse Event* CRF.

In case of subject death, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the Sponsor or CRO when available. Any other source documents related to the death should also be provided to the Sponsor or CRO. In the event that no source documents are available, the PI is required to describe the circumstances of the subject's death in a letter, e-mail or other written communication.

USADEs have special reporting requirements for both the investigator and Sponsor, as described in 21 CFR 812.150:

- Investigator Report: If a subject experiences an USADE, the investigator must notify Monteris and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
- Sponsor Report: USADEs will be reported to Food and Drug Administration (FDA), all reviewing IRBs, and participating investigators as soon as possible, but no later than 10 working days, after receiving notice of the USADE(s).

# 10 STATISTICS

## 10.1 Endpoint Analysis

Since the objective of this feasibility study is to characterize the performance of LITT, no formal hypotheses tests are planned for any endpoint. Descriptive statistics and exploratory analyses will be used in reporting outcomes for all endpoints.

### *10.1.1 Primary Endpoint: Analysis of Adverse Events*

For adverse events, both event counts and counts of subjects experiencing those events will be reported in tabular summaries. Rates will be reported based on the number of subjects experiencing one or more event as a proportion of all enrolled subjects and these subject rates will serve as the primary analysis.

Adverse event analysis may be repeated for events that occur after the initiation of treatment with rates calculated as a proportion of treated subjects, if it occurs that not all enrolled subjects undergo treatment with LITT.

Event counts, subject counts, and subject rates will also be reported for the following subsets of adverse events: SAE, SADE, UADE, USADE. Adverse events will be further characterized by tabulating the event severity and relationship (see section 9.1).

### *10.1.2 Primary Endpoint: Analysis of Neuropsychological Testing*

For each neuropsychological test, descriptive statistics will be reported for the measured score at baseline and each follow-up visit. In addition, change from baseline will be calculated at each follow-up visit and descriptive statistics will be reported. For each subject, the change from baseline will be categorized as improved, unchanged, or deteriorated based on whether the change exceeds a pre-specified threshold determined by Reliable Change Index (RCI) methodology for that specific neuropsychological test with a 95% confidence level. The threshold thus represents a degree of change that is unlikely (<2.5% chance in either direction) to occur due to measurement error of the neuropsychological instrument alone. The proportion of patients in each category at each follow-up time will be tabulated.

As there is no control group for comparison, any observed changes in neuropsychological function will need to be evaluated in comparison to longitudinal changes observed in prior longitudinal studies of similar subjects, examining typical changes in both subjects that have and have not undergone invasive therapy.

### *10.1.3 Secondary Endpoint: Analysis of Seizure Outcomes*

***Seizure frequency*** will be characterized by calculating the rate of seizure occurrence within specific follow-up time periods (count of reported events/reported time frame). Follow-up time periods of interest include all follow-up and between-visit follow-up periods (e.g., procedure to Month 3) to characterize the longitudinal course of seizure frequency. For each time period, descriptive statistics of subject-specific rates characterize the distribution of observed seizure rates. The change from baseline in seizure rates may also be calculated by calculating the difference in rates between a follow-up period and the baseline rate of seizures occurring prior to treatment (count of reported events/reported time frame). Since subjects may have different baseline seizure rates, the relative reduction (follow-up rate/baseline rate - 1) will also be calculated to scale the degree of improvement relative to the baseline rate. These analyses may be repeated for subsets of seizures with specific classifications to characterize the frequency of different seizure types.

The main analysis of seizure frequency will include subjects with at least 70 completed diary days in each 3-month period from procedure through 12 months and at least 140 diary days in each 6-month period from 12 months through study completion. To account for incomplete diary completion, sensitivity analyses may be performed by including subjects with less than the required level of diary completion and by using the number of days with completed diary entries to determine the denominator in the event rate calculation.

Seizure frequency may be further characterized by calculating the ***proportion of responders.*** A responder is a subject whose seizure frequency in a specified 3-month interval is reduced by ≥ 50% as compared to baseline.

***Seizure free days*** may be further characterized by calculating the number of seizure-free days that subjects experience during a specified 3-month interval. In order to make the 3-month

follow-up intervals comparable, the number of days actually recorded will be prorated to an 84-day intervals.

***Surgical outcome classification*** will be reported by tabulating the Engel and ILAE class frequency distribution at each scheduled follow-up among subjects completing that follow-up visit. The change in surgical classification between visits may be described by performing a cross-tabulation of the classifications at subsequent visits.

***Freedom from seizures* with altered awareness** will be reported using Kaplan-Meier curve analysis of the time to first seizure, as reported in patient diaries. The time to event analysis will exclude seizures that occur within the first 4 weeks post-procedure. The Kaplan-Meier analysis may be repeated for freedom from all seizures, seizures with other classifications, and inclusion of seizures within the first 4 weeks post-procedure. The log-log transformation will be used to calculate 95% confidence intervals. The time point of primary interest is 24 months.

### *10.1.4 Secondary Endpoint: Analysis of Quality of Life*

Quality of life is assessed with the QOLIE-31 instrument. QOLIE-31 scores at baseline and each scheduled follow-up visit will be characterized using descriptive statistics. In addition, the per-subject paired change from baseline will be calculated and descriptive statistics reported for each scheduled follow-up visit. These analyses may be repeated for the QOLIE-31 sub-domains.

Longitudinal analysis of the QOLIE-31 scores may be performed using a generalized estimating equation (GEE) repeated measures model with a working AR1 correlation structure to estimate the mean (with 95% confidence intervals) of the QOLIE-31 over time while accounting for within subject correlation. Baseline QOLIE-31 and visit (categorical) will be included as covariates in the model. The estimate of QOLIE-31 score at 24 months is of primary interest.

Finally, the proportion of subjects with a change from baseline in QOLIE-31 score of 13 points or more will be calculated at each follow-up visit. The threshold of 13 points is based on previous literature estimating 13 points of QOLIE-31 to be the minimum clinically important difference.[5] A 95% confidence interval for the proportion may be reported using the Clopper-Pearson exact method.

## 10.2 Statistical Analysis

### *10.2.1 General Principles*

Standard summary statistics will be calculated for all study variables to be reported. For continuous variables, statistics will include means, standard deviations, medians and ranges. Categorical variables will be summarized by frequency distributions.

[5] Wiebe S, Matijevic S, Eliasziw M, Derry PA. Clinically important change in quality of life in epilepsy. J Neurol Neurosurg Psychiatr 2002;73(2):116-120.

For any exploratory tests that are performed (e.g. change from baseline in endpoint measures), one-sided statistical tests will be deemed significant if the p-value is less than 0.025 while two-sided tests will be deemed significant if the p-value is less than 0.05. Statistical analyses will be conducted in SAS version 9.2 or above (SAS Institute, Cary, N.C.) or another validated statistical software package.

### *10.2.2 Analysis Populations*

All subjects enrolled in the study (including those withdrawn from the investigation) will be accounted for and documented.

The following analysis populations are defined:

Enrolled Set: All subjects enrolled in the study

Treated Set: All subjects that initiate treatment with LITT (received thermal delivery with the NBS)

Per-protocol Set: All subjects in the Treated Set that are treated according to the protocol requirements and meet study and treatment eligibility criteria

In the feasibility study setting, conclusions about performance are best informed by analyses of the Treated Set. Analyses may be repeated on the Enrolled Set for full reporting of study results and on the Per-protocol Set to provide insight into the potential impact of protocol deviations on the analysis results.

### *10.2.3 Handling of Missing Data*

The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Sensitivity analyses, such as multiple imputation or worst case imputation, may be performed to assess the robustness of study conclusions to the potential impact of missing data.

### *10.2.4 Sample Size*

For this feasibility study, there are no hypothesis tests and therefore sample size is not based on power. Rather, the sample size of 30 subjects is based on providing a sufficiently robust characterization of adverse events and other study endpoints. With a sample size of 30 subjects, adverse events that have a 5% probability per-subject have approximately an 80% chance of being observed in at least one subject in the study. Study results obtained from a sample of 30 subjects will permit planning for the potential range of results that could occur in a larger pivotal trial.

## 10.3 Interim Analysis

Analyses will be performed on data from baseline through a major study time point once all subjects have completed that major study time point (e.g., 6 months, 12 months and 24 months). There is

minimal opportunity for bias since all procedures will have been completed before any analysis occurs and all data will have been collected for a time point before analysis of that time point is conducted.

### 10.4 Handling of Deviations from the Protocol Statistical Plan

Any departure or deviation from these planned statistical methodologies will be documented and discussed in the Statistical Analysis Plan and will include the statistical rationale for divergence.

## 11 RISK/BENEFIT ANALYSIS

A risk analysis according to International Organization for Standardization (ISO) 14971 (Application of Risk Management to Medical Devices) has been conducted as part of the CE Marking process. Risks have been minimized or eliminated through appropriate design control, and confirmed by pre-clinical bench, laboratory and animal testing.

### 11.1 Risks

As with any surgical procedure, the NBS involves some risks. The following potential risks or discomforts may be associated with the surgical procedure or the NBS. In addition, the list includes possible risks associated with the use of the NBS in an epilepsy population.

The frequency and severity of adverse events can vary, and may necessitate additional medical intervention, including surgery.

- Agitation
- Anemia
- Brain aneurysm
- Anxiety
- Aphasia
- Ataxia or loss of body coordination
- Atelectesis
- Bacteremia or sepsis
- Bleeding into or around the brain
- Blurry vision/visual disturbance
- Cerebral infarction
- Coma
- Complete or incomplete hemiparesis
- Death
- Decreased energy
- Drowsiness
- Edema
- Failure of central regulation
- Fever
- Headache
- Hypertension
- Deep venous thrombosis
- Depression
- Difficulty hearing
- Difficulty speaking
- Difficulty swallowing
- Difficulty walking
- Hypotension
- Increased seizures frequency/duration or severity, new seizure type, or status epilepticus
- Infection, local or generalized
- Injury to blood vessels
- Injury to brain tissue
- Insomnia
- Intestinal toxicity
- Loss of mental function
- Muscle weakness
- Myocardial infarction
- Nausea/vomiting
- Nerve paralysis
- Obtundation
- Paralysis
- Personality or cognitive changes (e.g. mood, memory, attention and thinking ability)
- Permanent neurological deficit
- Pneumonia
- Pain at incision site
- Pulmonary or other air embolism
- Reaction to anesthesia or other drugs
- Stroke or transient ischemic attack (TIA)
- Sudden unexpected death in epilepsy (SUDEP)
- Thromboembolism
- Tingling or numb sensations in the body
- Tissue damage
- Unconsciousness
- Wound dehiscence

Additional possible risks from the evaluations required during this study (but not directly related to the use of the NBS) include:

**Laboratory Testing Risks**

For the pregnancy test, a blood sample will be taken by inserting a needle into a vein in the arm. Some risks of this procedure include fainting, infection, bruising, formation of a blood clot, pain, and/or bleeding at the site of the needle puncture.

**Pregnancy Risks**

The effects of LITT during pregnancy are unknown, and it is possible that harmful side effects could occur to both the mother and unborn child. For this reason, pregnant subjects are excluded from participation in this study. If the subject is a woman of childbearing age capable of becoming pregnant, they will be given a pregnancy test prior to entry into the study and again prior to the procedure.

**Neuropsychological Testing Risks**

The neuropsychological tests are either computer tests or paper and pencil tests. None of these tests pose any significant risk, although some persons may find the testing tedious or even frustrating. The testing, which can take up to 3 hours to perform, may be spread over two days. Breaks may be included during the testing to make it easier to complete.

**MRI Risks**

MRI uses large magnet fields. There are no known or foreseeable risks or side effects associated with MRI scanning procedures except for those people who have electrically, magnetically or mechanically activated implants, or metal in or on their bodies. A MRI scan is not uncomfortable but those prone to claustrophobia (fear of enclosed spaces) may become anxious.

**Contrast Dye (Gadolinium) Risks**

A contrast dye, gadolinium, may be used for the MRI. Possible side effects of a gadolinium injection include mild headache, nausea, and local pain, low blood pressure and lightheadedness. Very rarely, patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

## 11.2 Methods to Minimize Risk

To mitigate the risks above, Monteris will work with neurosurgeons trained specifically in NeuroBlate techniques, train all study personnel and provide device labeling that contains all precautions, warnings and contraindications. The loud knocking sound during the MRI may be dimmed with the wearing of earplugs.

## 11.3 Benefits

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the study device may have the following benefits:

- The subject may experience a decrease in seizure frequency
- The subject may experience an improvement in their quality of life
- The subject may experience an improvement in their neuropsychological functioning

## 11.4 Alternative Treatment

There is no obligation for a subject to take part in this study. Alternative treatments may include:

- Undergoing the LITT procedure without participation in the study
- Undergoing a different surgical intervention (other than LITT)
- Continued medical (non-surgical) management

Each subject's doctor will inform the subject as to what alternative methods are available.

# 12 ADMINISTRATIVE PROCEDURES

## 12.1 Contact Information

The CRO will maintain a document with the contact information for all clinical study personnel participating in the study, including those listed below:

- Sponsor
- CRO
- Sites (principal investigator (PI), sub-investigator(s), study coordinators, neuropsychologists, and IRB chairperson
- Core Laboratory
- DSMB
- CEC

### *12.1.1 Sponsor*

The Sponsor contact for the study is:

Daryle Petersen, Vice President, Clinical Affairs
Monteris Medical, Inc.
16305 36th Avenue North, Suite 200
Plymouth, MN 55446, USA
Email: dpetersen@monteris.com
Telephone: 763-253-4714
Mobile: 612-308-3371

### *12.1.2 Contract Research Organization (CRO)*

The CRO contact for this study is:

Joan Hazen, Study Director
BRIGHT Research Partners
3100 West Lake Street, Suite 420
Email: joan@brightresearchpartners.com
Telephone: 612-345-4544
Mobile: 612-327-3221

### *12.1.3 MRI Core Laboratory*

The MRI core laboratory for the study is:

Medical Metrics, Inc.

2121 Sage Rd. Suite 300, Houston, TX 77056
Telephone: 713-850-7500
Fax: 713-850-7527

## 12.2 Site Selection

The Sponsor and/or CRO will assess each potential Site to ensure the investigators and his/her staff meet the following criteria:

- The Site is a current user of the NeuroBlate System
- The Site has an epileptologist that can act as principal investigator
- The Site has a neurosurgeon with experience using LITT for MTLE/MTS epilepsy patients
- The investigators are qualified by experience and training
- The Site has a neuropsychologist/neuropsychometrist
- The Site has adequate support staff responsible for fulfilling the clinical study requirements specified in the study protocol
- The Site is a level III or level IV epilepsy center based on the National Association of Epilepsy Center's guidelines
- The Site has experience doing epilepsy clinical studies
- The Site has adequate access to epilepsy patients specified in the study protocol
- The Site is not participating in another laser-based MTLE/MTS epilepsy clinical study that is currently enrolling subjects; studies that have completed enrollment and are in the subject follow-up phase would not exclude the site from participation in the FLARE study.
- The investigators are not on the FDA disqualified or debarred list

## 12.3 Site Training

Site personnel will be trained per the study-specific Training Plan. All Site personnel will undergo training prior to performing any study-related procedures. All training will be documented.

Existing Site personnel who have been delegated *new* tasks and new Site personnel will undergo training as designated in the Training Plan.

## 12.4 Records and Reports

### *12.4.1 Responsibilities of the Sponsor*

The Sponsor and CRO are responsible for maintaining study records and reports per applicable ICH GCP, federal regulations, ISO 14155, and applicable standard operating procedures (SOPs), and study-specific plans (e.g., Monitoring Plan, Data Management Plan, Training Plan, and Statistical Analysis Plan).

### *12.4.2 Responsibilities of the Investigator*

The investigator will maintain the following accurate, complete, and current records relating to their participation in the study:

- All correspondence which pertains to the investigation

- Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated ICFs and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records will include:
  - Documents evidencing the informed consent process. The case history for each individual will document that informed consent was obtained prior to participation in the study.
  - All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests
  - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol
- Signed Investigator Agreements, financial disclosure agreements, PI protocol signature pages, and curriculum vitaes
- IRB approval documents, including approval of protocol, protocol amendments and ICFs

The investigator is responsible for the preparation, review, signature, and submission of the reports listed below in Table 3.

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**Table 3: Investigator Reporting Responsibilities**

| Report | Submitted to | Description |
|---|---|---|
| Unanticipated Serious Adverse Device Effects (USADE) | Sponsor/CRO & IRB | Notification within 10 working days after the investigator first learns of the effect. |
| Serious Adverse Events | IRB | Per IRB reporting requirements |
| Withdrawal of IRB approval | Sponsor/CRO | Notification within 5 working days of withdrawal. |
| Progress Report | Sponsor/CRO & IRB | Periodic report detailing the progress of the study, occurring at least annually. |
| Deviations from protocol (CFR 812.150) | | |
| *Emergency Use* | Sponsor/CRO & IRB | Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). |
| *Other* | Sponsor/CRO & IRB | If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), prior approval must be obtained from Monteris, the reviewing IRB, and FDA when required. |
| Failure to obtain informed consent | Sponsor/CRO & IRB | Notification within 5 working days |
| Final Report | Sponsor/CRO & IRB | Submitted within 3 months after termination or completion of the investigation. |

## 12.5 Study Documentation

### *12.5.1 Case Report Forms*

Study data will be collected using CRFs in an electronic data capture system. Further information regarding CRFs is found in the study-specific CRF Completion Guidelines.

### *12.5.2 Record Storage and Retention*

The investigator will maintain all study documentation as outlined in the Clinical Trial Agreement.

### *12.5.3 Data Management*

Study data will be managed as outlined in the study-specific Data Management Plan.

## 12.6 Study Monitoring

Each Site will be monitored by the Sponsor and/or CRO to ensure that the study is conducted in compliance with the protocol, and in accordance with good clinical practices, CRO SOPs and the study-specific Monitoring Plan.

## 12.7 Ethical Conduct of the Study

This study is to be conducted in accordance with US and international standards for good clinical practice, as described in the following documents:

- International Conference on Harmonisation Guidelines for Good Clinical Practice (1996)
- US Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 50, 54 and 56 and 812)
- ISO 14155: 2011

## 12.8 Institutional Review Board

The Site must submit the protocol and ICF to the IRB and will forward a copy of the written approval to the CRO. The study (study number, protocol title, and version), documents approved (e.g., protocol, ICF) and the date of the review should be clearly stated on the IRB approval documentation, and the approval must be signed by the IRB Chair. The Site will not be activated to enroll subjects until a copy of written and dated approval has been received by the CRO and other applicable study activation requirements (as outlined in the Monitoring Plan) are complete.

The Site must submit any protocol or ICF amendments to the IRB and is required to forward a copy of the written approval to the CRO. The IRB should also be informed of any event likely to affect the safety of subjects or the conduct of the study.

The ICF must be reviewed by the CRO prior to submission to the IRB for approval.

## 12.9 Protocol Deviations

A protocol deviation is defined as a circumstance in which the investigator or other Site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (e.g., Clinical Trial Agreement or Investigator Agreement).

Every attempt will be made to adhere to the protocol. However, should an investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice will be given to the Sponsor or CRO as soon as possible, but no more than 5 working days from the date the emergency occurred. With the exception of an emergent circumstance, prior approval from the Sponsor and the IRB is required for any change in, or deviation from, the protocol as such changes may affect the scientific soundness of the protocol or the rights, safety, and welfare of study subjects.

Protocol deviations will be documented on the *Protocol Deviation* CRF. Deviations are reportable to the Institution's governing IRB during the annual reporting process, unless otherwise directed by the governing IRB requirements.

## 12.10 Study Discontinuation

The Sponsor reserves the right to terminate or suspend the study for valid scientific reasons or reasons related to the protection of subjects (e.g., the discovery of an unexpected, significant, or unacceptable

risk to subjects). The Sponsor may also terminate or suspend the study if the stopping rules (as defined in the DSMB charter) have been met.

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all investigators of the termination or suspension and the reason(s). The IRB will also be informed, either by the Sponsor or investigator, and provided with the reasons(s) for the termination or suspension. If applicable, regulatory authorities will be informed.

The IRB may choose to discontinue the study at any Site for which they granted approval if the research study is not conducted in accordance with the IRB's requirements or the research study indicates unexpected serious harm to subjects.

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## APPENDIX A MEDICATIONS

All prescription medications (epilepsy and non-epilepsy) that the subject is taking during the course of the trial will be recorded on a CRF. Epilepsy medications will be recorded on the *Epilepsy Medication Log* CRF. Non-epilepsy medications will be recorded on the *Concomitant Medication Log* CRF. Documentation of perioperative medications and anesthetic agents is only required for steroids and for medications used to treat an intraoperative adverse event.

Additionally, all epilepsy medications that the subject took in the year preceding the Baseline visit will be recorded on the *Epilepsy Medication Log* CRF. Collection of retrospective rescue medication use is not required.

**AEDs**

No changes in AED total daily doses are allowed between the Baseline visit and the Month 12 visit with the following exceptions: (1) temporary periprocedural discontinuation or modification for clotting considerations (e.g., valproic acid/valproate), (2) if the clinical condition of the subject warrants modification/discontinuation.

If there is a change, record the changes on the *Epilepsy Medication CRF* and document on a *Protocol Deviation CRF.*

**Acute (Rescue) AEDs**

In many epilepsy centers, a standard of care for uncontrolled epilepsy is the use of intermittent “rescue” medications (e.g., acute benzodiazepines). These medications are used by the subject on an “as needed” basis to either abort a prolonged seizure or to prevent a cluster of seizures from occurring. If the protocol excluded subjects who used rescue medications the subject pool would decrease substantially. Therefore, the protocol will allow the use of rescue medications during the study. Rescue medications will be recorded on the *Epilepsy Medication* CRF.

## APPENDIX B SEIZURE CLASSIFICATION AND SUBJECT DIARY

### Seizure Classification

At the Baseline visit, the investigator or authorized delegate will collect seizure information from the subject and/or caregiver. Information about each seizure type will be collected on a *Seizure Classification - Initial* CRF. Based upon the definition provided by the subject/caregiver, the investigator will classify the seizure based on the International League Against Epilepsy (ILAE) definitions (see Table 4). As subjects may experience multiple kinds of seizures within one class (e.g., two kinds of simple partial seizures), each seizure will be assigned a *seizure letter*. Seizure letters will be assigned alphabetically starting with A.

**Table 4: Seizure Classification (International League Against Epilepsy)**

| |
|---|
| **Focal Seizures** |
| Without impairment of consciousness or responsiveness |
| With observable motor or autonomic components |
| Involving subjective sensory or psychic phenomena only |
| With impairment of consciousness or responsiveness |
| Evolving to a bilateral, convulsive seizure |
| |
| **Generalized Seizures** |
| Absence |
| Typical |
| Atypical |
| Myoclonic absence |
| Eyelid myoclonia |
| Myoclonic |
| Myoclonic |
| Myoclonic atonic |
| Myoclonic tonic |
| Tonic |
| Clonic |
| Tonic clonic |
| Atonic |
| |
| **Unclassified Seizures** |
| Epileptic spasms – focal or generalized |
| Seizure type is unclassified |

If at any time during the study the subject experiences a new type of seizure, a new *Seizure Classification - Initial Report* CRF and an *Adverse Event* CRF will be completed. A *Seizure Classification - Update* CRF will be completed if there are any *changes* to previously reported seizure types. At a minimum, the *Seizure Classification - Update* CRF will be completed for each seizure type at the Month 3, Month 6, and Month 12 visits.

**Retrospective Seizure Data Collection**

Retrospective seizure frequency data will be collected at the Baseline visit. Retrospective reporting will be based on the subject's seizure history and, if available, a subject diary. Although 3 months of seizure frequency data is needed to determine eligibility, seizure count data for the 12 months prior to baseline will be collected, if available.

**Diary**

The Sponsor will provide a standard diary on which the subject and/or caregiver can record seizure activity. Each diary contains the following information:

- A "key" to the seizure types correlating the assigned seizure letter to the subject's usual descriptor of the seizure (e.g., Seizure Type A = the "big one")
- A calendar to record daily seizure activity and missed AED doses
- Other relevant information (e.g., new type of seizure)

Subjects may prefer to use their own diary format (paper or electronic); these will be allowed as long as the subject's diary collects the information listed above.

Subjects may also use the diary to record the following (although this information may be elicited by direct questioning of the subject during a study visit):

- Changes to epilepsy and non-epilepsy medications
- Use of rescue medications
- Recording of non-study-related visits to the doctor, hospital or emergency room.
- Comments section to record other relevant information (e.g., new type of seizure)

**Instruction for Diary Completion**

At the Baseline visit, and again prior to discharge, the investigator or authorized delegate will instruct the subject/caregiver on proper diary completion. This instruction will include:

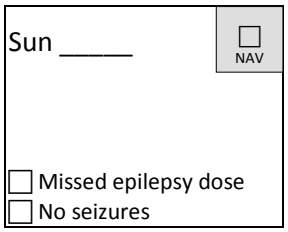
- Importance of accurate diary-keeping
- Explanation of the seizure classification key
- How to complete the diary:
    - Recording of seizure activity
    - If no seizures occurred on that day, the subject will be instructed to tick the "no seizure" box for that day
    - If subject missed any dose(s) of their epilepsy medications, the subject will be instructed to tick the "missed epilepsy dose" box for that day
    - Explanation that the NAV (not available) designation on a calendar day is for investigator use only
    - How to record medication changes and use of rescue medications
    - How to record non-study-related visits to the doctor, hospital or emergency room
    - What might be recorded in the "other" section

**Recording Seizures**

Subjects or their caregiver will keep a seizure diary starting the day after discharge. A new diary is provided at subsequent appointments. The subject or caregiver will record the number and type of seizures each day.

Sites will be instructed to take measures to ensure that diary entries are faithfully recorded in order to minimize missing diary data. Subjects will be trained on the importance of accurate diary-keeping.

At each visit the investigative staff will review the diary with the subject and/or caregiver and address any concerns with diary completion. If seizure information is not available for a specific diary day, the coordinator will tick the "NAV" box for that day. An example of a diary day is shown below.




**Diary Compliance**

In order to minimize missing diary data, sites will be instructed to take measures to ensure that diary entries are faithfully recorded. At each visit the investigative staff will review the diary with the subject and/or caregiver and address any concerns with diary completion. The investigator will also provide additional training to new caregivers over the course of the trial, as needed.

**Diary Data**

The seizure information collected on the diaries will be recorded on a *Diary Summary* CRF. Any additional information recorded on the diary (e.g., about changes in the subject's epilepsy medications, the use of rescue medications, and adverse events) will also be recorded on the applicable CRFs.

## APPENDIX C NEUROPSYCHOLOGICAL TESTING

This study will include a **core** neuropsychological battery as well as a **supplementary** battery.

The tests in the **core battery** were chosen based on the following criteria:

1) they are recommended by the National Institute of Neurological Disorders and Stroke (NINDS) as common data elements in studies of the neuropsychological effects of epilepsy and its treatments[6],
2) they assess a broad range of cognitive domains that might plausibly be affected by a novel surgical approach or post-surgical complications,
3) they assess domains commonly affected by temporal lobe dysfunction,
4) the threshold for a statistically reliable decline have been defined in prior studies,[7,8, 9, 10] and
5) valid analogue versions are available in Spanish.[11]

The core battery does not include a test of non-verbal or visual memory because such measures are unlikely to be sensitive to LITT effects in the non-dominant temporal lobe, and verbal memory measures should be sufficiently sensitive to these effects. Despite occasional positive results in smaller, selected samples, larger studies and meta-analyses[12, 13, 14] have failed to provide consistent evidence that standardized neuropsychological measures of visual memory are sensitive to non-dominant temporal dysfunction. Rates of statistically reliable changes (improvements and declines) on visual memory tests do not differ between dominant and non-dominant temporal lobe resections, suggesting that these tests are non-specific indicators of temporal lobe dysfunction. On the other hand, approximately 20% of patients show reliable declines after non-dominant temporal lobectomy on verbal memory tests.[15]

Minimally invasive neurosurgical approaches have the potential to reduce sub-acute cognitive morbidity associated with the trauma of craniotomy and extensive resection and allow for a more rapid return to full functioning. Therefore, we further recommend that a subset of cognitive domains that are dependent on temporal lobe dysfunction be assessed by a *supplementary* battery administered at the Baseline, Month 3, Month 6 and Month 12 visits. Assessment of cognitive outcomes is typically

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[6] https://commondataelements.ninds.nih.gov/epilepsy.aspx#tab=Data_Standards

[7] Martin RC, Sawrie SM, Gilliam F, Mackey M, Faught E, Knowlton R, Kuzniekcy R. Determining reliable cognitive change after epilepsy surgery: development of reliable change indices and standardized regression-based change norms for the WMS-III and WAIS-III. *Epilepsia*. 2002;43(12):1551-1558.

[8] Martin RC, Sawrie SM, Roth DL, Gilliam FG, Faught E, Morawetz RB, Kuzniecky R. Individual memory change after anterior temporal lobectomy: a base rate analysis using regression-based outcome methodology. *Epilepsia*. 1998;39(10):1075-1082.

[9] Sawrie SM, Chelune GJ, Naugle RI, Lüders HO. Empirical methods for assessing meaningful neuropsychological change following epilepsy surgery. *J Int Neuropsychol Soc.* 1996;2(6):556-564.

[10] Hermann BP, Seidenberg M, Schoenfeld J, Peterson J, Leveroni C, Wyler AR. Empirical techniques for determining the reliability, magnitude, and pattern of neuropsychological change after epilepsy surgery. *Epilepsia*. 1996;37(10):942-950.

[11] Barr, WB., Bender., H., Morrison, C., Cruz-Laureano, D., Vazquez, B., & Kuzniecky, R. Diagnostic validity of a neuropsychological test battery for Hispanic patients with epilepsy. *Epilepsy & Behavior.* 2009;16:479-483.

[12] Vaz SA. Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. *Seizure.* 2004;13: 446–452.

[13] Barr WB, Chelune GJ, Hermann BP, Loring DW, Perrine K, Strauss E, Trenerry MR, Westerveld M. The use of figural reproduction tests as measures of nonverbal memory in epilepsy surgery candidates. *J Int Neuropsychol Soc.*1997;3:435-443.

[14] Barr WB. Examining the right temporal lobe's role in nonverbal memory. *Brain and Cognition.* 1997;35:26–41.

[15] Sherman EMS, Wiebe S, Fay-Mcclymont TB, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia*. 2011;52(5):857–869.

performed at 6-12 months postoperatively to provide an estimate of long-term outcome, because most biologically-based recovery occurs by that time. However, word-retrieval deficits are particularly notable in the immediate post-operative period and resolve to varying degrees over time. [16, 17]. Patients in cognitively-demanding jobs are often encouraged to remain out of work for several months following resective surgery while these sub-acute problems resolve. Therefore, any LITT-based reduction in sub-acute cognitive morbidity may be missed by relying only on assessments at Months 6 and 12.

The tests in the **supplementary battery** were chosen based on the following criteria:

1) they assess cognitive abilities (naming, verbal memory, semantic knowledge) that are known to depend on intact temporal lobe function;
2) multiple forms are available (or can be readily constructed from available stimuli) to minimize practice effects across visits; and
3) content does not overlap with tests in the core battery (to avoid enhancing practice effects on the core battery and maintain comparability of the core battery's results to prior studies that have relied on a single post-operative assessment).

   *NOTE: Validated versions of the supplementary battery are limited to the English language format, making the supplementary battery available only for subjects tested in English.*

A brief description of all tests is outlined below. The test schedule for both English and Spanish-speaking subjects is provided in Table 5 and Table 6, respectively.

**Core Battery – English-Speaking Subjects**

Wechsler Adult Intelligence Scale-IV (WAIS-IV)

The WAIS-IV is a general test of intelligence developed to measure cognitive ability in adults. The WAIS can be administered in 60-90 minutes and yields a full-scale IQ (FSIQ), general ability index (GAI) and 4 index scores: verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI) and processing speed index (PSI).

Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT is a verbal learning and memory test that consists of a list of 15 words which an examiner reads aloud at the rate of one per second. The subject's task is to repeat all the words he or she can remember, in any order. This procedure is carried out a total of five times. Then the examiner presents a second list of 15 words, allowing the subject only one attempt at recall. Immediately following this, the subject is asked to remember as many words as possible from the first list. This is followed by a yes/no recognition trial, where subjects are asked to distinguish the 15 original words from 15 distractor words. Completion time is estimated at 15 minutes.

16 Langfitt JT, Rausch R. Word-finding deficits persist after left anterotemporal lobectomy. *Arch Neurol.* 1996;53(1):72-76.

17 Stafniak P, Saykin AJ, Sperling M, Kester MS, Robinson LJ, O'Connor MJ, Gur R. Acute naming deficits following dominant temporal lobectomy: Prediction by age at 1st risk for seizures. *Neurology*. 1990;40:1509–1512.

Boston Naming Test-60 (BNT-60)

The 60-item BNT is a visual confrontation naming test sensitive to deficits in semantic retrieval. The BNT contains 60 line drawings graded in difficulty. Subjects are required to verbally name pictures (line drawings) of common objects. Items are rank ordered in terms of their ability to be named, which is correlated with their frequency. This test is appropriate for adults.

Controlled Oral Word Association Test (COWAT)

The COWAT uses the three letter set of F, A, and S to assess phonemic fluency. Individuals are given 1 minute to name as many words as possible beginning with one of the letters. The procedure is then repeated for the remaining two letters.

Animal Naming Test

The animal naming test is a category fluency test that measures impairment in verbal production, semantic memory and language. The subject is asked to verbally name as many animals as they can in a 60 second time period.

Trail Making Test

The test consists of two parts and requires a subject to 'connect-the-dots' of 25 consecutive targets on a sheet of paper or computer screen as fast as possible while still maintaining accuracy. If the subject makes an error, the test administrator is to correct them before the subject moves on to the next dot. The goal of the test is for the subject is to finish the part A and part B as quickly as possible. The time taken to complete the test is used as the primary performance metric. Part A is used primarily to examine cognitive processing speed. Part B is used to examine executive functioning.

Grooved Pegboard Test

The Grooved Pegboard is a manipulative dexterity test. This unit consists of 25 holes with randomly positioned slots. Pegs, which have a key along one side, must be rotated to match the hole before the peg can be inserted. This test requires more complex visual-motor coordination than most pegboards. Completion time is estimated at 20 minutes.

**Supplementary Battery – English-Speaking Subjects Only**

Logical Memory Test

This is a set of brief stories based on the Wechsler Memory Scale Logical Memory subtest developed specifically for use in studies using a repeated paradigm.-[18] Subjects are read a paragraph-length story at a rate of one idea per second. Following completion of the story, subjects are asked to repeat as much of that story as they can. Each word item recalled in 30 seconds scores two points for “immediate recall” regardless of the order of recall. The paragraph is read one more time and patients are asked to

[18] Cunje A, Molloy DW, Standish TI, Lewis DL. Alternate forms of logical memory and verbal fluency tasks for repeated testing in early cognitive changes. *Int Psychogeriatr*. 2007;19(1):65-75.

remember the paragraph. After a delay period, subjects are asked to recall the paragraph once again, providing a "delayed recall" score. The estimated time for this test is five minutes.

Auditory Naming Test

A set of 15 test items will be drawn from the 50-item form developed by Hamberger, et al.[19]
The auditory naming test requires examinees to name concrete items described orally.

Visual Naming Test

A set of 15 test items will be drawn from the 50-item form developed by Hamberger, et al.[19]
Visual naming requires the naming of 30 line drawings or parts thereof (e.g., telephone, telephone dial).

Verbal Fluency Test

Versions of this test will be derived by the forms developed by Cunje et al [18] specifically for use in studies using a repeated paradigm. In verbal fluency tests, participants have to say as many words as possible from a category in a given time (usually 60 seconds).

**Table 5: Neuropsychological Testing Requirements for English-Speaking Subjects**

| Test | | Baseline [1] | Month 3 | Month 6 | Month 12* | Early Withdrawal |
|---|---|---|---|---|---|---|
| **CORE** | | | | | | |
| WAIS-IV | | X | | | X | X |
| RAVLT | | X | | | X | X |
| BNT-60 | | X | | | X | X |
| COWAT | | X | | | X | X |
| Animal Naming | | X | | | X | X |
| Trail Making | | X | | | X | X |
| Grooved Pegboard | | X | | | X | X |
| **SUPPLEMENTARY** | | | | | | |
| Logical Memory | | Form 1 | Form 2 | Form 3 | Form 1 | |
| Auditory Naming | | Form 1 | Form 2 | Form 3 | Form 1 | |
| Visual Naming | | Form 1 | Form 2 | Form 3 | Form 1 | |
| Verbal Fluency | | Form 1 | Form 2 | Form 3 | Form 1 | |

[1] Prior neuropsychological testing may be used for baseline values if the testing was conducted within 6 months prior to the baseline visit and there were no significant changes to the subject's AEDs or changes to the subject's clinical condition that may affect cognitive function.

**Core Battery – Spanish-Speaking Subjects**

Raven's Standard Progressive Matrices (SPM)™ Test

Raven's SPM is a test commonly used as a nonverbal means to estimate intelligence level in non-English speaking subjects. It will be used as an IQ estimate for Spanish-speaking subjects participating in this study. The test assesses observation skills and clear-thinking ability. It offers insight about someone's capacity to observe, solve problems, and learn. The test has a total of 60 items presented in 5 sets (A–E), with 12 items per set. The Raven's SPM produces a single raw score as well as percentile rank to indicate

[19] Hamberger MJ, Seidel WT. Auditory and visual naming tests: normative and patient data for accuracy, response time, and tip-of-the-tongue. *J Int Neuropsychol Soc.* 2003;9(3):479-489.

the candidate's educative ability or the ability to think clearly and extract meaning out of events, compared to a norm group.

WHO-UCLA Auditory Verbal Learning Test (AVLT)

This is version of the RAVLT paradigm modified for non-English-speaking subjects. The Spanish translation will be used for Spanish-speaking subjects participating in this study. Like the RAVLT, it is a verbal learning and memory test that consisting of a list of 15 different words, which an examiner reads aloud at the rate of one per second. The subject's task is to repeat all the words he or she can remember, in any order. This procedure is carried out a total of five times. Then the examiner presents a second list of 15 words, allowing the subject only one attempt at recall. Immediately following this, the subject is asked to remember as many words as possible from the first list. This is followed by a yes/no recognition trial, where subjects are asked to distinguish the 15 original words from 15 distractor words. Completion time is estimated at 15 minutes.

Ponton-Satz Boston Naming Test (PS-BNT)

The PS-BNT is a modified version of the Boston Naming Test consisting of 30 items from the original BNT selected by experts on the basis of appropriateness for the use with Spanish speakers. As in the English version, subjects are required to verbally name pictures (line drawings) of common objects. Items are rank ordered in terms of their ability to be named, which is correlated with their frequency.

Controlled Oral Word Association Test (COWAT)

The COWAT uses the three letter set of F, A, and S to assess phonemic fluency. Individuals are given 1 minute to name as many words as possible beginning with one of the letters. The procedure is then repeated for the remaining two letters. (The procedure used for Spanish-speaking subjects is identical to the procedure used for English-speaking subjects.)

Animal Naming Test

The animal naming test is a category fluency test that measures impairment in verbal production, semantic memory and language. The subject is asked to verbally name as many animals as they can in a 60 second time period. (The procedure used for Spanish-speaking subjects is identical to the procedure used for English-speaking subjects.)

Color Trails Test

This is a version of the commonly used Trail Making Test, modified for use with non-English-speaking subjects. The Color Trails Test assesses sustained attention and divided attention in adults. Numbered circles are printed with vivid pink or yellow backgrounds that are perceptible to color-blind individuals. For Part 1, the respondent uses a pencil to rapidly connect circles numbered 1-25 in sequence. For Part 2, the respondent rapidly connects numbered circles in sequence, but alternates between pink and yellow. The length of time to complete each trial is recorded, along with qualitative features of performance indicative of brain dysfunction, such as near-misses, prompts, number sequence errors, and color sequence errors.

Grooved Pegboard Test

The Grooved Pegboard is a manipulative dexterity test. This unit consists of 25 holes with randomly positioned slots. Pegs, which have a key along one side, must be rotated to match the hole before the peg can be inserted. This test requires more complex visual-motor coordination than most pegboards. Completion time is estimated at 20 minutes. (The procedure used for Spanish-speaking subjects is identical to the procedure used for English-speaking subjects.)

**Table 6: Neuropsychological Testing Requirements for Spanish-Speaking Subjects**

| Test | | Baseline [1] | Month 3 | Month 6 | Month 12 | Early Withdrawal |
|---|---|---|---|---|---|---|
| **CORE** | | | | | | |
| Raven's Matrices | | X | | | X | X |
| WHO-UCLA AVLT | | X | | | X | X |
| Ponton-Satz BNT | | X | | | X | X |
| COWAT | | X | | | X | X |
| Animal Naming | | X | | | X | X |
| Color Trails | | X | | | X | X |
| Grooved Pegs | | X | | | X | X |

[1] Prior neuropsychological testing may be used for baseline values if the testing was conducted within 6 months prior to the specific baseline visit and there were no significant changes to the subject's AEDs or changes to the subject's clinical condition that may affect cognitive function.

## APPENDIX D SURGICAL OUTCOME CLASSIFICATIONS

The two surgery outcome classifications used in this study, the Engel system[20] and ILAE system,[21] are presented in Table 7 and Table 8.

The occurrence of early postoperative seizures or auras in the first week after epilepsy surgery is relatively common and may result from the effects of the acute surgical injury (termed "neighborhood" seizures). As such, both the Engel class I and the ILAE class 1 exclude "early" seizures. The Engel classification is not specific for the exact time period (first few weeks postoperative), whereas the ILAE classification excludes seizures in the first 4 weeks. *For the purposes of this study, seizures occurring in the first 4 weeks postoperative will be excluded when evaluating both the Engel and ILAE classes*.

An additional ILAE classification, 1a, is available for those that have been seizure- and aura-free since surgery (as recommended by Wieser et al).

**Table 7: Engel Surgical Outcome Classification**

| |
|---|
| **Class I: Free of disabling seizures** |
| A: completely seizure-free since surgery |
| B: non-disabling simple partial seizures only since surgery |
| C: some disabling seizures after surgery, but free of disabling seizures for at least 2 years |
| **Class II: Rare disabling seizures ("almost seizure-free")** |
| 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** |
| A: worthwhile seizure reduction |
| B: prolonged seizure-free intervals amounting to greater than half the follow-up period, but not < 2 years |
| **Class IV: No worthwhile improvement** |
| A: significant seizure reduction |
| B: no appreciable change |
| C: seizures worse |

[20] Engel J Jr, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J Jr, editor. Surgical treatment of the epilepsies. New York: Raven Press; 1993:609-21.

[21] Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia 2001;42:282–6.

## Table 8: ILAE Surgical Outcome Classification

**Class 1:** Completely seizure-free; no auras
***Class 1a:*** *Completely seizure- and aura-free since surgery*
**Class 2:** Only auras[1]; no other seizures
**Class 3:** One to three seizure days[2] per year; ± auras
**Class 4:** Four seizure days per year to 50% reduction of baseline seizure days[3]; ± auras
**Class 5:** Less than 50% reduction of baseline seizures days to 100% increase of baseline seizure days; ± auras
**Class 6:** More than 100% increase in baseline seizure days; ± auras

[1] Auras are only counted if they are short in duration and similar or identical to the preoperative auras.
[2] A "seizure day" (for the purposed of this classification) is defined as a 24-hour period with one or more seizures. This may include an episode of status epilepticus.
[3] The number of "baseline seizure days" is calculated by determining the seizure-day frequency during the 12 months before surgery, with corrections for the effects of AED reduction during diagnostic evaluations prior to the index procedure.