EASEE II – Clinical Investigation Plan

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EASEE II – A pilot study to assess the feasibility of neurostimulation with the EASEE® System to treat medically refractory focal epilepsy

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SPONSOR SIGNATURE PAGE

EASEE II – A pilot study to assess the feasibility of neurostimulation with the EASEE® System to treat medically refractory focal epilepsy

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INVESTIGATOR SIGNATURE PAGE

EASEE II – A pilot study to assess the feasibility of neurostimulation with the EASEE® System to treat medically refractory focal epilepsy

I have read the EASEE II Clinical Investigation Plan (CIP) and agree to adhere to the requirements outlined within. I will provide all pertinent information regarding the CIP to the study personnel under my supervision. I will review and discuss this material with them and ensure they are fully informed of the requirements of this CIP. I will also ensure that this study is conducted in compliance with this CIP, Good Clinical Practice (GCP), EN ISO 14155 and any applicable local and/or national regulatory agencies and their requirements.

Investigator/Sub-investigator Name (print): _____

Date (*dd.mm.yyyy*): _____

Signature: _____

Contents

1 Revision History

Lists details of all protocol amendments whenever a new version of the protocol is produced.

Protocol Version No.	Date	Author(s) of changes	Modification Description
1.0	16-Apr-2018	Kinga Egressy	Initial Protocol Version
2.0	24-Apr-2018	Kinga Egressy	• Registered Trade Mark (®) added across document. • 9.6 Configuration: "Stimulation protocol (Table 2)" replaced by "EASEE® Stimulation Protocol"

2 Synopsis

Full Title EASEE II – A pilot study to assess the feasibility of neurostimulation with the EASEE® System to treat medically refractory focal epilepsy
Running Title EASEE II
Study Design This is a first-in-human, prospective, interventional, unblinded, multicenter study designed to collect data on 15 subjects implanted with the EASEE® System.
Study Objectives Primary study objective: The primary study objective is to demonstrate the safety of the EASEE® System in subjects with medically refractory focal epilepsy. Secondary study objectives: 1. Assess changes from baseline seizure frequency 2. Assess changes from baseline seizure severity 3. Assess changes from baseline EEG 4. Assess changes from baseline quality of life 5. Assess changes from baseline mood 6. Assess changes from baseline neurocognition
Device Description The EASEE® (Epicranial Application of Stimulation Electrodes for Epilepsy) System is an implantable stimulation device, which is indicated for the treatment of medically refractory focal epilepsy. The EASEE® System consists of the implantable components EASEE® Power (IPG) and EASEE® Lead (electrode array and connecting link), none of which have the CE Mark. The surgical tools include EASEE® Template (tool for determining implant location) and a torque wrench which do not have the CE Mark, a screw/screwdriver set used to fix the array onto the skull and a tunneler, which have the CE Mark. The external control elements include EASEE® Set (physician programmer), EASEE® Connect (telemetry wand), EASEE® Magnet and EASEE® Access, none of which have the CE Mark. All study personnel must complete training on study procedures before implanting and programming the EASEE® System.
Intended Use The EASEE® System is indicated for use as an adjunctive therapy in reducing the burden of epilepsy in adults with focal onset seizures that are refractory to two or more antiepileptic medications.
Rationale This is a pilot study to explore the feasibility of neurostimulation with the EASEE® System in a small

patient collective. This is the first time that the EASEE® System is implanted in subjects, therefore primarily safety, but also preliminary efficacy aspects of treatment with the EASEE® System will be evaluated.

Patient Population

Patients with a clinical diagnosis of medically refractory focal epilepsy. Potential patients include those eligible based on the inclusion/exclusion criteria and willing to undergo implantation with the EASEE® System.

Study Duration

Total duration of the study is 17 months, including 1 month of baseline monitoring, 1 month of post-implant recovery, 3 months of evaluation period and 12 months of follow-up.

Key Inclusion Criteria:

Patients enrolled in the study must meet all of the following criteria:

1. Patients with a clinical diagnosis of focal seizures or focal to bilateral tonic clonic seizures.
2. Patients with a diagnosis of lateral temporal lobe epilepsy or extra-temporal lobe epilepsy.
3. Patients with a predominant epileptic focus, which can be clearly identified as the site of implantation for the electrode based on EEG and clinical presentation.
4. Patients who have failed treatment with a minimum of two anti-seizure medications (used in appropriate doses).
5. Patients having seizures which are distinct, stereotypical events and can be reliably counted, in the opinion of the Investigator, by the patient or caregiver and recorded in a seizure diary.
6. Patients having an anticipated average of 3-300 partial-onset seizures (focal to bilateral tonic clonic seizures) during the baseline period.
7. Patients taking a constant dose of antiepileptic medication(s) over the most recent 28-day period prior to the baseline period (use of medication for acute treatment of seizures is allowed).
8. Patients between the ages of 18 and 75 years.
9. Patients able and willing to provide appropriate consent prior to study procedures.
10. Patients able to complete regular office appointments per the protocol requirements, including behavioral (mood) surveys and neuropsychological testing.
11. Patients willing to be implanted with the EASEE® System as a treatment for his/her seizures.

Key Exclusion Criteria:

Patients who meet any of the following criteria are not eligible to be enrolled in the study:

1. Patients with a diagnosis of mesial temporal lobe epilepsy.
2. Patients with a previous diagnosis of psychogenic or non-epileptic seizures, which are semiologically non-distinguishable from epileptic seizures.
3. Patients with a diagnosis of primarily generalized seizures.
4. Patients with unprovoked status epilepticus in the preceding 6 months prior to enrolment.

5. Patients with a clinically significant or unstable medical condition (including cardiac conditions, alcohol and/or drug abuse) or a progressive central nervous system disease.
6. Patients with a diagnosis of active psychosis, major depression or suicidal ideation in the preceding year (excluding postictal psychosis).
7. Females who are pregnant or have a pregnancy wish in the next 2 years.
8. Patients enrolled in a therapeutic investigational drug or device trial.
9. Patients who are anatomically not eligible for EASEE® System implant in the opinion of the Investigator.
10. Patients who have had resective surgery to treat epilepsy in the target region of implantation.
11. Patients with an implanted electronic medical device that delivers electrical energy to the body (e.g. VNS, DBS, cardiac pacemeaker or defibrillator).
12. Patients requiring scheduled MRIs during the study phase.
13. Patients who are unable, or do not have the necessary assistance, to properly operate the EASEE® Access handheld device.

Endpoints

Primary Endpoint

The primary endpoint is the safety of the EASEE® System evaluated at 4 months post-implant.

Secondary Endpoints

1. Seizure frequency: baseline seizure frequency and responder rate compared to respective values at 4 months, 8 months and 16 months post-implant.
2. Seizure severity: baseline seizure severity compared to seizure severity at 8 months and 16 months post-implant.
3. Epileptiform activity: baseline measurements of scalp EEG compared to data collected at 1 month, 8 months and 16 months post-implant.
4. Quality of life: baseline subject rated quality of life compared to 8 months and 16 months post-implant.
5. Mood: baseline subject rated mood compared to 8 months and 16 months post-implant.
6. Neurocognition: baseline neurocognition compared to 8 months and 16 months post-implant.

Study Procedures and Measurements

The main study phases and respective procedures are as follows:

Screening

Subjects will be screened according to the pre-defined inclusion and exclusion criteria. If all criteria are met and the informed consent form has been signed, then the subject is considered as enrolled in the EASEE II study. In case daily recorded seizure data is not available for at least one month prior to this timepoint, then the patient should proceed to the baseline period.

Baseline Period

During the 1-month baseline period, subjects are requested to record daily seizure data in seizure diaries. At the conclusion of this period, the implant eligibility criteria will be reviewed.

Implantation

The EASEE® System will be implanted after the baseline period has been completed and the implant eligibility criteria have been met. EASEE® Lead will be implanted over the predominant focus, as identified by the physician. Following implantation of EASEE® Lead and EASEE® Power, technical testing of the device will be performed to confirm that the implantation has been successful.

Recovery

There will be a post-operative recovery period of 1 month to ensure that healing processes can take place. The device will remain off during this period.

Configuration

After the 1-month recovery period the device will be configured individually for each subject by the treating physician according to EASEE® Stimulation Protocol 1 and the stimulation will be turned on.

Evaluation Period

The evaluation period begins after configuration of the device at 1 month post-implant and lasts for a duration of 3 months. Stimulation will remain on during this time. At 4 months post-implant the primary safety endpoint will be analysed.

Follow-up Period

At 8 months post-implant the Investigator will evaluate the benefit for the subject in agreement with the Sponsor:

- If it is deemed that the subject has benefited from the stimulation i.e. there is a reduction in the burden of epilepsy in terms of reduction in seizure frequency and/or severity, and/or improvement in QoL, neurocognition and the subject wishes to receive further stimulation, then the device may remain active up to the end of the follow-up period. If wished by the subject and at the discretion of the treating physician, one EASEE® Power replacement shall be provided by the Sponsor during this time in case of battery depletion.
- If there has been no documented positive effect of stimulation, but the subject wishes to receive further stimulation, then the stimulation parameters may be changed at the discretion of the treating physician. If the subject does not wish further stimulation, then the device will be inactivated. If wished by the subject and at the discretion of the treating physician, one EASEE® Power replacement shall be provided by the Sponsor during this time in case of battery depletion.
- At any point during the study or after study completion all implanted components may be removed at the discretion of the physician and patient.

There will be a safety visit at 12 months post-implantation and the final visit will take place at 16 months post-implantation. Other than the above visits, the subjects will not be required to visit the clinic more often than for their routine treatment.

The data to be collected during each phase is outlined in Table 1. EASEE II Data Collection Table

Statistical Considerations

This is a prospective, interventional, unblinded, multicenter study. The statistical population to be investigated is defined according to the intended use of the investigational device, as well as the inclusion and exclusion criteria of the study. As a first in human study, the primary endpoints were chosen to be safety related and will assess probability of overall SAEs. Secondary endpoints are efficacy related and will assess probability of benefit to the patient.

Sample Size: 15 subjects will be recruited. The primary goal of the study is to generate data regarding the feasibility and performance of neurostimulation with the EASEE® System. The results of this feasibility study will aid in the planning of a larger, sufficiently powered CE-Mark trial. Allowing for a conservative 20% dropout, there will be a total of 12 subjects, which meets the threshold for a sufficiently precise estimate of several factors to be used in future studies.

	Screening/ Inclusion	Eligibility/ Implantation	Configuration/ Stimulation ON	End of Evaluation Period	Treatment Evaluation Visit	Follow-up	Final Visit
Timing (in months relative to implantation)	-1	0	+1	+4	+8	+12	+16
Visit Window		+2 weeks	±1 week	±2 weeks	±2 weeks	±1 month	±1 month
Informed Consent	X						
Inclusion/Exclusion	X	X					
Demographics	X						
Medical History	X						
Pregnancy Test		A					
Drug Log	X	X	X	X	X	X	X
Scalp EEG (1 hour recording)		X	X		X		A
Seizure Diary	X*	X	X	X	X	X	X
Seizure Severity (SSQ)		X			X		X
Quality of Life (QOLIE-31-P)		X			X		X
Depression Inventory (NDDI-E)		X			X		X
Neurocognition		X			X		X
Device Parameters		X	X	X	X	X	X
Device Interrogation		X	X	X	X	X	X
Adverse Events/Device Deficiency		X	X	X	X	X	X
Study Completion							X

X required activity
X* completed retrospective diary accepted, if available
A activity to be completed as needed

Table 1 EASEE II Data Collection Table

3 Introduction

3.1 Background

Epilepsy is a recurrent tendency to spontaneous, intermittent, abnormal electrical activity in the brain, manifesting as seizures. It is a common neurological disorder affecting approximately 1 % of the population (Longmore M et al., 2014). Epileptiform discharges involve either a localized area of the brain resulting in a focal seizure or the entire brain resulting in a generalized seizure. In adults, the most common type is focal epilepsy (Panebianco M et al., 2015). The majority of patients has a good prognosis to achieve satisfactory seizure control by treatment with anti-epileptic drugs (AEDs).

The goal of antiepileptic drugs is seizure control, which means reduction of seizure frequency and/or severity to the point that the patient is able to live a normal lifestyle without epilepsy-related limitations and with minimal or no drug toxicity (Greenberg MS, 2016). Drug choice depends on seizure type and epilepsy syndrome, other medication, co-morbidities and patient preference (Longmore M et al., 2014). The majority of epileptic patients has a good prognosis to achieve satisfactory seizure control by treatment with a single AED (Panebianco M et al., 2015). However, in 20 – 30 % of patients, seizures are not effectively controlled by monotherapy and often require treatment with a combination of different AEDs (Panebianco M et al., 2015). A failure of monotherapy indicates an 80 % chance that seizures will not be controllable pharmacologically. Indeed, only 10 % of patients benefit significantly from the addition of a second drug (Greenberg MS, 2016) and the chance to achieve complete seizure control with subsequent trials of antiepileptic drug is less than 5% (Brodie et al., 2012). In contrast, increased drug load, due to polytherapy in patients non-responsive to antiepileptic treatment in monotherapy, often leads to an increased rate of medication-related adverse effects, such as cognitive impairment or mood disturbance (Eddy et al., 2011).

Therefore, despite aggressive medical management with AEDs, seizures are not effectively controlled in 20 – 30 % of patients (Panebianco M et al., 2015). Non-pharmacological treatments are becoming increasingly attractive as a way to improve seizure control and to improve quality of life of patients with pharmacoresistant epilepsy. Epilepsy surgery is one option with high success rates; However, the procedure can be performed only in a limited number of patients and carries risks for cognitive decline specific to the regions of the brain which have been resected or disconnected (Loring DW et al., 2015). For those who are not surgical candidates or those who continue to have seizures after surgery, neurostimulation may offer an alternative treatment option (Sprengers M et al., 2014, Salanova V et al., 2015; Stefan H et al., 2012).

Over the last 20 years, the clinical efficacy of electrical stimulation of the vagus nerve and deep brain structures for the treatment of several neurologic and psychiatric conditions, including epilepsy, depression, and Parkinson disease, has been extensively investigated (Varga ET et al.,

2011; Sohal VS and Sun FT, 2011). Both extracranial, including vagus nerve and transcranial direct current stimulation, as well as intracranial stimulation, comprising deep brain and cortical stimulation, have been applied as adjunctive treatment options for medically refractory epilepsy. Despite their potential clinical benefit, the mechanisms by which deep brain stimulation and other forms of neurostimulation modulate neuronal activity remain unknown (Sohal VS et al., 2011).

Depending on the invasiveness of the procedure, as well as on the location of the electrodes (extracranial or intracranial), different neurostimulation techniques are associated with specific adverse events. Vagus nerve implantation and stimulation is primarily associated with hoarseness (4.9 to 66.3 %, Ghani S et al., 2015), cough (7.3 to 45.3 %, Klinkenberg S et al., 2012 and Ghani S et al., 2015), dyspnea (1.7 to 25.3 %, Ghani S et al., 2015), pain (1.6 to 30.1 %, Klinkenberg S et al., 2012; Ghani S et al., 2015; Ryvlin P et al., 2014), paresthesia (4.9 to 25.2 %, Klinkenberg S et al., 2012 and Ghani S et al., 2015), nausea (14.7 to 20.4 %, Ghani S et al., 2015) and headache (2.4 to 24.2 %, Klinkenberg S et al., 2012; Ghani S et al., 2015; Ryvlin P et al., 2014). The majority of adverse events associated with implantation of deep brain or subdural electrodes and intracranial stimulation occur in the first months following device implantation. Adverse events include implant site infection (3.7 to 12.7 %, Heck CN et al., 2014; Bergey GK et al., 2015; Salanova V et al., 2015), implant site pain (23.6 %, Salanova V et al., 2015), paresthesia including tingling, vibration or shocking sensations at the stimulator implant site (9.3 to 22.7 %, Fisher R et al., 2010 and Salanova V et al., 2015), neurostimulator migration (5.5 %, Salanova V et al., 2015), lead migration or damage (2.6 to 8.2 %, Heck CN et al., 2014; Bergey GK et al., 2015; Salanova V et al., 2015), memory impairment (7.3 to 13.0 %, Salanova V et al., 2015 and Fisher R et al., 2010), dizziness (5.6 to 6.4 %, Fisher R et al., 2010 and Salanova V et al., 2015). Furthermore, intracranial stimulation is associated worsening of depression symptoms (3.1 to 14.8 %, Bergey GK et al., 2015 and Fisher R et al., 2010).

Non-implantable stimulation therapy, such as cathodal transcranial direct current stimulation (tDCS) is a non-invasive and safe brain stimulation method to suppress regional cortical excitability. Although currently tDCS is not FDA-approved for clinical use, clinical data indicates that tDCS may offer a practical therapeutic option for the treatement of epilepsy, with the benefit of an easy, rapid and focal application (Larkin M et al., 2016; Auvichayapat N et al., 2013; Varga ET et al., 2011). Indeed tDCS is associated with few and relatively mild side effects compared to the implanted stimulation systems. These include mild itching sensation during the stimulation, mild headache (San-Juan D et al., 2017; Karvigh SA et al., 2017; Assenza G et al., 2016) and transient erythematous rash under the reference electrode (3.7 %, Auvichayapat N et al., 2013).

In epilepsy drug trials, a ≥50 % reduction in seizure frequency is often used as the outcome measure to assess treatment efficacy (Chambers A and Bowen JM, 2013). Similarly, this measure is the most commonly reported seizure frequency outcome in clinical trials investigating the performance of neurostimulation devices as adjunctive therapy in medically refractory epilepsy. All neurostimulation techniques are associated with a positive benefit/risk profile in patients with medically refractory epilepsy, and a significant decrease in seizure frequency with a reduction of

≥50 % has been demonstrated for VNS (Panebianco M et al., 2015; Chambers A and Bowen JM, 2013; Ghani S et al., 2015), ATN DBS (Salanova V et al., 2015; Lee KJ et al., 2012) and responsive neurostimulation (Bergey GK et al., 2015; Heck CN et al., 2014). Furthermore, several studies showed that tDCS compared to sham stimulation significantly reduces the number of epileptiform discharges and/or seizure frequency in patients with medically refractory epilepsy with a single epileptogenic focus (San-Juan D et al., 2017; Assenza G et al., 2016; Auvichayapat N et al., 2013; Fregni F et al., 2006).

Electrical stimulation is an invasive procedure and therefore a greater reduction in seizure frequency should be expected. On the other hand, the intended patient population has limited treatment options as patients have medically refractory epilepsy and are not candidates for epilepsy surgery. Therefore any reduction in seizure frequency can be considered as clinically meaningful (Chambers A and Bowen JM, 2013).

3.2 Rationale

This is a pilot study to explore the feasibility of neurostimulation with the EASEE® System in a small patient collective. This is the first time that the EASEE® System is implanted in humans, therefore primarily safety, but also preliminary efficacy aspects of treatment with the EASEE® System will be evaluated.

4 Objectives

Primary study objective:
The primary study objective is to demonstrate the safety of the EASEE® System in subjects with medically refractory focal epilepsy.

Secondary study objectives:

1. Assess changes from baseline seizure frequency
2. Assess changes from baseline seizure severity
3. Assess changes from baseline EEG
4. Assess changes from baseline quality of life
5. Assess changes from baseline mood
6. Assess changes from baseline neurocognition

5 Protocol

5.1 Study Design

This is a first-in-human, prospective, interventional, unblinded, multicenter study designed to collect data on 15 subjects implanted with the EASEE® System. Good Clinical Practices shall be followed during the study, including Declaration of Helsinki, EN ISO 14155, WMO and MEDDEV 2.7.1.

5.2 Number of Subjects/Sites

Up to four clinical sites will be asked to enrol a collective total of 15 subjects. Each site will be asked to enrol a minimum of 2 subjects, however inability to meet the minimum will not constitute a protocol deviation. There will be no upper limit for enrolment, as long as the overall study sample size is not exceeded. The enrolment period for the study is anticipated to be approx. 6 months.

5.3 Study Duration

The total duration of the study is 17 months, including 1 month of baseline monitoring, 1 month of post-implant recovery, 3 months of evaluation period and 12 months of follow-up.

5.4 Inclusion Criteria

Patients enrolled in the study must meet all of the following criteria:

1. Patients with a clinical diagnosis of focal seizures or focal to bilateral tonic clonic seizures.
2. Patients with a diagnosis of lateral temporal lobe epilepsy or extra-temporal lobe epilepsy.
3. Patients with a predominant epileptic focus, which can be clearly identified as the site of implantation for the electrode based on EEG and clinical presentation.
4. Patients who have failed treatment with a minimum of two anti-seizure medications (used in appropriate doses).
5. Patients having seizures which are distinct, stereotypical events and can be reliably counted, in the opinion of the Investigator, by the patient or caregiver and recorded in a seizure diary.
6. Patients having an anticipated average of 3-300 partial-onset seizures (focal to bilateral tonic clonic seizures) during the baseline period.
7. Patients taking a constant dose of antiepileptic medication(s) over the most recent 28-day period prior to the baseline period (use of medication for acute treatment of seizures is allowed).
8. Patients between the ages of 18 and 75 years.
9. Patients able and willing to provide appropriate consent prior to study procedures.
10. Patients able to complete regular office appointments per the protocol requirements, including behavioral (mood) surveys and neuropsychological testing.

11. Patients willing to be implanted with the EASEE® System as a treatment for his/her seizures.

5.5 Exclusion Criteria

Patients who meet any of the following criteria are not eligible to be enrolled in the study:

1. Patients with a diagnosis of mesial temporal lobe epilepsy.
2. Patients with a previous diagnosis of psychogenic or non-epileptic seizures, which are semiologically non-distinguishable from epileptic seizures.
3. Patients with a diagnosis of primarily generalized seizures.
4. Patients with unprovoked status epilepticus in the preceding 6 months prior to enrolment.
5. Patients with a clinically significant or unstable medical condition (including cardiac conditions, alcohol and/or drug abuse) or a progressive central nervous system disease
6. Patients with a diagnosis of active psychosis, major depression or suicidal ideation in the preceding year (excluding postictal psychosis).
7. Females who are pregnant or have a pregnancy wish in the next 2 years.
8. Patients enrolled in a therapeutic investigational drug or device trial.
9. Patients who are anatomically not eligible for EASEE® System implant in the opinion of the Investigator.
10. Patients who have had resective surgery to treat epilepsy in the target region of implantation.
11. Patients with an implanted electronic medical device that delivers electrical energy to the body (e.g. VNS, DBS, cardiac pacemeaker or defibrillator).
12. Patients requiring scheduled MRIs during the study phase.
13. Patients who are unable, or do not have the necessary assistance, to properly operate the EASEE® Access handheld device.

The following criteria must be met for the subject to be considered as enrolled:

1. All inclusion and exclusion criteria are satisfied at the screening visit
2. Informed Consent has been correctly obtained and properly documented on the Informed Consent Form.

The following criteria must be met for the subject to be implanted:

1. The subject continues to meet the inclusion and exclusion criteria directly prior to implantation (i.e. between successful screening/consent and implantation). If any criteria are not met, then the subject will be considered as a screening failure. All screening failures will be documented on a screening log.

All subjects who are considered as enrolled and have undergone the implantation procedure will be analysed for safety and efficacy parameters. Subjects with unsuccessful implant attempt will undergo a 1 month safety follow-up post-implant and can be terminated from the study once any

reported adverse event (if applicable) has resolved or stabilized. Given the nature of the study as a first in human trial, and the restricted number of subjects to be enrolled, whenever an unsuccesful implantation will occur, the subject will be replaced by a next enrolled subject, so that data from a minumum of 12 subjecs will be available for analysis.

5.6 Discontinuation and Replacement of Subjects

Each subject who is enrolled and treated should remain in the clinical trial until completion of the required follow-up period. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without prejudice. Should this occur, the reason for withdrawal must be documented in the subject medical record. A subject may be discontinued from study treatment at any time if the subject or the Investigator feels that it is not in the subject's best interest to continue.

Conceivable reasons for discontinuation may include, but are not limited to the following:

Subject Withdrawal:	Subject participation in a clinical trial is voluntary and the subject may discontinue participation (refuse all subsequent testing/ follow-up) at any time without loss of benefits they would be otherwise entitled to.
Investigator Termination:	Investigator may terminate the subject´s participation without the subject´s consent if the Investigator believes it´s medically necessary.
Lost to Follow-up:	Subject does not complete the scheduled follow-up visits, but has not "officially withdrawn" from the trial (this does not apply to missed visits).

If a subject is withdrawn from treatment, due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

5.6.1 Lost-to-Follow-up

Site personnel should make all reasonable efforts to locate and communicate with subjects at each contact time point. If there is difficulty contacting the subject, a minimum of two telephone calls to contact the subject should be recorded in the source documents, including date, time, and initials of site personnel trying to make contact. If these attempts are unsuccessful, a letter should be sent to the subject. If the subject misses two consecutive scheduled contact time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

5.6.2 Study Discontinuation

The Study Completion/Discontinuation Form must be completed when:

- the subject is considered lost to follow-up (per the above definition) before the 16 months follow-up time point has been reached *or*
- the subject withdraws from the study *or*
- the Investigator withdraws the subject from the study *or*
- the subject has completed the study (at 16 months post-implant).

The Sponsor shall be notified of the reason for subject discontinuation. The site will provide this information on the Study Completion/Discontinuation Form (e-CRF) and on source documents. Investigators must also report this to their EC if defined by their institution's procedure.

5.6.3 Replacement of Subjects

The following rules are in place for the replacement of subjects:

- subjects with an unsuccessful implantation will be replaced by a next enrolled subject to ensure a min. of 12 subjects are available for further analyses.
- subjects who withdraw from the study will not be replaced as they are already accounted for in the estimated drop out rate.

6 Risk Analysis

6.1 Potential Risks

The potential hazards and harms have been identified by conducting the Questionnaire of EN ISO 14971, Annex C, D and E. Detailed results can be found in the EASEE II Investigator's Broschure and/ or Instructions for Use for this section. The risks associated with the implantation of the EASEE® System can be classified into the following main categories:

- Risks related to the surgical procedure
- Risks related to electrical stimulation
- Risks related to device failure

6.2 Potential Benefits

The Sponsor and the Investigators have determined that this study is justified, based on the potential benefit to subject's quality of life by a possible reduction in the frequency and/or severity of the epileptic seizures or other relevant parameters.

Additional potential benefits of participating in the EASEE II study include:

- Information from this study may provide data that can lead to further improvement of the EASEE® System or even other potential treatments for epilepsy, thus benefitting patients in the future.

- Patients participating in the EASEE II study may in some cases receive treatment with the EASEE® System sooner than patients who do not participate in the study, as they will not have to wait for approval and reimbursement of the device.

6.3 Risk-Benefit Analysis

Based on the available clinical data on currently applied neurostimulation techniques, a positive risk-benefit profile for the EASEE® System, as an adjunctive therapy for medically refractory focal epilepsy can be expected. Due to the fact that the electrode array of the EASEE® System will be implanted extracranially in the subgaleal area, the implantation procedure is less invasive, and is therefore assumed to be associated with a considerably lower risk of implantation-related adverse events compared to intracranial implantation. The efficacy of the EASEE® System is expected to be similar to other neurostimulation techniques. Safety and preliminary efficacy of the EASEE® System will be investigated in the course of the EASEE II trial, which will be conducted by Precisis according to Council Directive 90/385/EEC for active implantable medical devices.

Despite the risks of all epilepsy treatments, the risks of doing nothing are often greater. Patients with a higher frequency of seizures have poorer cognitive function, a significant increase in anxiety, depression and suicidality and a poorer employment status, lower quality of life and worse overall health compared to patients with fewer seizures. A reduction in seizure frequency and/or severity, even without seizure freedom, can improve mood, employment, perceived health and quality of life. These observations reinforce the need for alternative therapies, which can reduce the burden of seizures (Heck CN et al., 2014).

7 Device Description

7.1 EASEE® System Description

The EASEE® (Epicranial Application of Stimulation Electrodes for Epilepsy) System is an implantable stimulation device, which is indicated for the treatment of patients with medically refractory focal epilepsy.

7.1.1 Implantable Components

The sterile components developed for the EASEE® System and intended for implantation are EASEE® Lead and EASEE® Power. These are shown below in Figure 1.

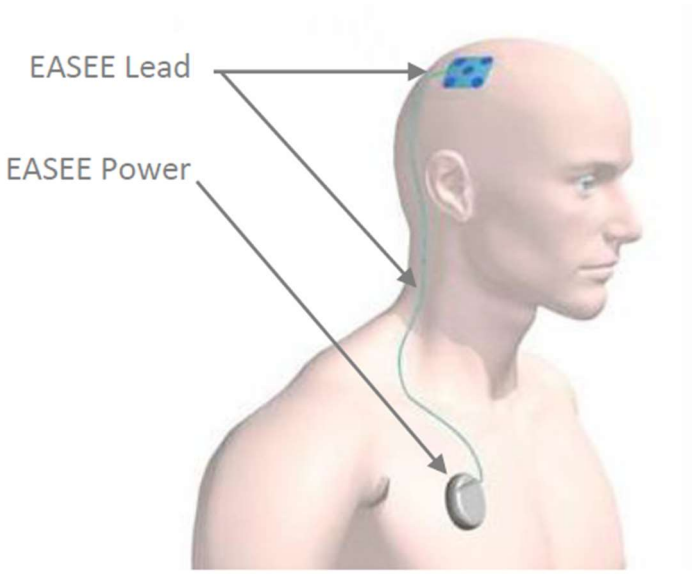

Figure 1 **Implantable components of the EASEE® System**

EASEE® Lead, Model EALE00

EASEE® Lead consists of a specialized electrode array on the distal side and a connector on the proximal side. Both are linked by a non-detachable lead body. The array consists of five electrodes arranged in a pseudo-Laplacian form, with a central electrode surrounded by four peripheral electrodes allowing precise targeting of defined brain areas. The array of EASEE® Lead is implanted between the subject's scalp and skull, in the so-called subgaleal area, while the lead body is tunneled subcutaneously from the head to the chest and connected to EASEE® Power. EASEE® Lead is manufactured by Precisis AG and is not CE-Marked.

EASEE® Power, Model EAPW00

EASEE® Power is a generator of electrical pulses which is implanted in the thorax, caudal to the clavicle. It is equipped with batteries and stimulation control electronics. The header of EASEE® Power contains the connector block for connecting EASEE® Lead, as well as an radio frequency (RF) antenna to communicate with the external control components. EASEE® Power is manufactured by Precisis AG and is not CE-Marked.

7.1.2 Surgical Accessories

The surgical accessories are used during the implantation and are all supplied in a sterile form:

Tunnelling tool

The tunnelling tool is used by the neurosurgeon to aid the subcutaneous routing of the link of EASEE® Lead between the skull and the chest. The tunnelling tool has not been developed by Precisis AG and is already CE-Marked. Medtronic Tunneler Model 3655-38 will be used.

Fixation screws and screwdriver

Screws are needed to fix the array of EASEE® Lead onto the skull. Two types of screws have been defined and the corresponding screwdriver is also provided. These components have not been developed by Precisis AG and are already CE-Marked. Stryker self-drilling Screws 56-15904S4 and 56-17304S1 and Stryker Handle Medium 65-15002 with Stryker Blade Long 65-15003 will be used.

Torque wrench, 8C-65-209X-X-00

A torque wrench is needed in order to enable the mechanical fixation between EASEE® Lead and EASEE® Power. This is manufactured by Precisis AG, with the reference number 8C-65-209X-X-00.

EASEE® Template, 8C-61-015X-X-00

EASEE® Template is provided to the surgeon to check the prepared implantation site for the array of EASEE® Lead prior to implantation. Thus dimension and accessability of the electrode areas can be tested without risks of mechanical damage to the implant. EASEE® Template is manufactured by Precisis AG, with the reference number 8C-61-015X-X-00.

7.1.3 External Control Components for the Physician

These external control components allow trained medical personnel to set the stimulation parameters according to the individual needs of the subject, as well as to test the functionality of EASEE® Power (battery life, impedance). There are three components:

EASEE® Connect, Model EACT00

EASEE® Connect is a compact device which enables RF communication between EASEE® Set and EASEE® Power. It is manufactured by Precisis AG and is not CE-Marked.

EASEE® Set, Model EASE00

The software used to program EASEE® Power will be pre – installed on a tablet PC. Both, the software application and the tablet are referred to as EASEE® Set. The software has been developed by Precisis AG and is not CE-Marked.The tablet PC has not been developed by Precisis AG and is already CE-Marked. Model Mio Care L130 from Mitac International Corp, with reference number 5420027523972 will be used.

EASEE® Magnet, Model EAMA00

The activation magnet has two functions

1. Wake-up EASEE® Power at the first use
2. Re-activate EASEE® Power after stimulation has been deactivated using EASEE® Set

EASEE® Magnet is manufactured by Precisis AG and is not CE-Marked.

7.1.4 External Control Component for the Patient

EASEE® Access, Model EAAC00

This external control component is known as EASEE® Access and allows the subject to communicate with the implantanted device. The following functionalities are available within the EASEE II study:

1. Turn stimulation off
2. Check battery life of EASEE® Power
3. Check battery life of EASEE® Access

EASEE® Access is manufactured by Precisis AG and is not CE-Marked.

7.2 Indication

The EASEE® System is indicated for the treatment of medically refractory focal epilepsy.

7.3 Manufacturers

The legal manufacturer of the EASEE® System is Precisis AG:

Precisis AG
Hauptstr. 73
69117 Heidelberg
Germany
Tel: +49(0)6221 6559300
Fax: +49(0)6221 6559310
info@precisis.de

7.4 Device Training

The training of the Investigators and appropriate clinical site personnel will be the responsibility of Sponsor and/or designee and may be conducted during a site initiation visit, or other appropriate training sessions.

8 Endpoints

8.1 Primary Endpoint

The primary endpoint is the safety of the EASEE® System evaluated at 4 months post-implant. Safety is defined as follows:

- Acute safety: Incidence of SAEs for the surgical implant procedure and the following month.
- Short-term chronic safety: Incidence of SAEs for the surgical implant procedure and the following 4 months.

8.2 Secondary Endpoints

1. Seizure frequency: baseline seizure frequency and responder rate (defined as at least 50% reduction in seizure rate from baseline) compared to values at 4 months, 8 months and 16 months post-implant.
2. Seizure severity: baseline seizure severity compared to seizure severity at 8 months and 16 months post-implant.
3. Epileptiform activity: baseline measurements of scalp EEG will be collected and compared to data collected at 1 month, 8 months and 16 months post-implant.
4. Quality of life: baseline subject rated quality of life compared to 8 months and 16 months post-implant.
5. Mood: baseline subject rated mood compared to 8 months and 16 months post-implant.
6. Neurocognition: baseline neurocognition compared to 8 months and 16 months post-implant.

9 Study Procedures

9.1 Overview

The different phases of the study are shown in Figure 2 below:

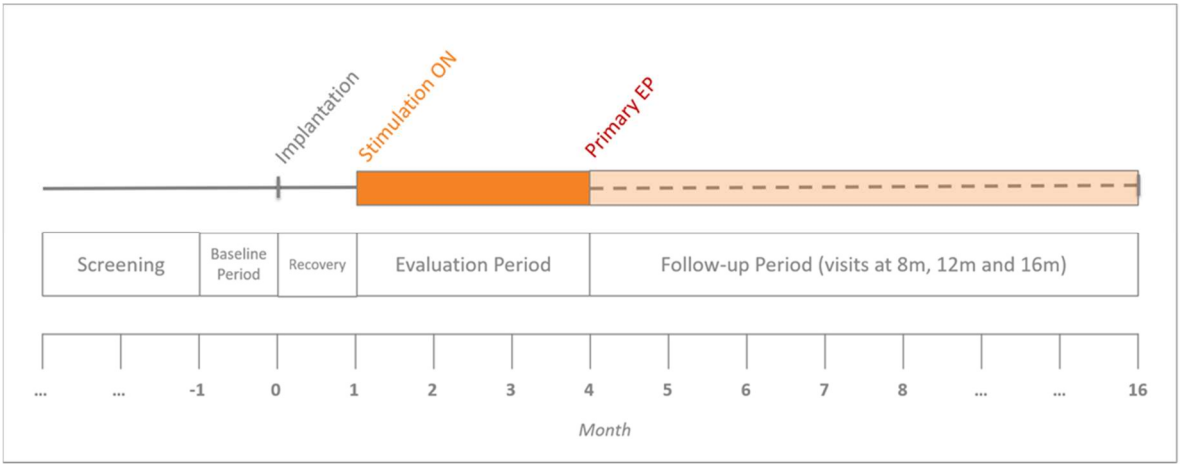

Figure 2 **Study Phases and Timelines**

9.2 Screening and Informed Consent

9.2.1 Screening

Subjects planned to be included in the EASEE II study should be screened for eligibility by study staff members as delegated to this task after having been trained on the Clinical Investigation Plan. Subjects who do not meet the inclusion and exclusion criteria will not be enrolled in this clinical investigation. Screening failures will be captured on a screening log. Subjects meeting the inclusion and exclusion criteria will be asked to sign an informed consent form. “Non-routine”

assessments, which are specific to the clinical investigation cannot be done before an informed consent form has been signed.

The following data will be collected at screening:

- Demographic data
- Medical history
- Epilepsy history
- Seizure frequency
- Antiepileptic medication

After successful screening the subject will be requested to give informed consent to participate in the study.

9.2.2 Informed Consent

Clinical investigation-specific procedures cannot be started until a signed informed consent has been obtained. The Investigator or a designee appointed by the Investigator who has been trained on the Clinical Investigation Plan, will explain the nature and scope of the clinical investigation, potential risks and benefits of participation, and answer any questions that the subject may have. All subjects and Investigators must sign , date and time the Ethics Committee (EC)-approved informed consent prior to any clinical trial/investigation-specific procedure. No subjects belonging to a vulnerable population, or dependant on the Investigator or Sponsor (e.g., subordinate hospital staff or Sponsor staff) or subjects unable to read or write will be enrolled. The obtaining of the informed consent, provision of a copy to the subject, along with the date and time must be documented in the subject's medical records. In addition, the signed informed consent must be kept in the subject's medical records or in the study site file and a copy must be given to the subject.

9.2.3 Point of Enrollment

The subject is considered as enrolled in the trial at the time he/she has signed and dated the patient informed consent.

9.2.4 Retrospective Seizure Diary Data

At enrollment the patient will be asked if he/she is able and willing to provide a seizure diary with daily recording of seizures for at least one month prior to this timepoint. If the treating physician assesses this diary as complete and reliable, then the obtained data will be used to replace the baseline period or to extend the data obtained during the baseline period for up to 3 months prior to enrollment. In case it is decided by the treating physician that the 1 month baseline period is needed to collect reliable and accurate seizure frequency data, then the patient should proceed to the baseline period.

9.3 Baseline Period

During the 1-month baseline period, subjects will be provided with seizure diaries and will be requested to record daily seizure data. At the conclusion of this period, the implant eligibility criteria will be reviewed. Subjects who fail to meet implant eligibility criteria, will be captured on a screening log and are considered as screening failure subjects . Only the data of subjects who have undergone the implantation procedure will be included in the analysis report for safety and efficacy.

9.4 Implantation

9.4.1 Implant Eligibility

The EASEE® System will be implanted after the 1-month baseline period has been completed and the implant eligibility has been reviewed and met. Only when the following implant eligibility criteria are met, may the subject proceed to implantation:

1. Seizure frequency as specified in the inclusion criteria
2. Constant AEDs as specificed in the inclusion criteria
3. No pregnancy

9.4.2 Baseline Testing

After implant eligibility has been established subjects will undergo baseline testing (see Table 1: Data Collection Table). The following data will be collected:

1. Patient surveys: in addition to the retrospective seizure frequency data collected for up to 3 months prior to enrollment, the subject will be asked to conduct a seizure diary for the complete duration of the study i.e. 16 months. Furthermore subjects will be requested to complete the Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P) survey, the Seizure Severity Questionnaire (SSQ), the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) questionnaire and neurocognitive tests (for example EpiTrack®).
2. Scalp EEG: a one-hour EEG-recording during wakefulness will be completed for each subject to establish baseline values. Note: the EASEE® System must be switched off for all EEG recordings occurring post-implant to prevent interference.
3. Determination of implantation site for EASEE® Lead: the implantation site for EASEE® Lead will be determined based on existing diagnostic data such as EEG, clinical presentation etc.. EASEE® Lead will be implanted over the predominant focus, as identified by the physician. This should also be documented in the patient chart.

A blood assessment will be completed prior to the implantation procedure as per standard of care. No study-specific blood assessment is required.

9.4.3 Surgery

Once the implantation site has been determined (see above) the neurosurgeon will mark the implantation site to ensure that the central electrode of the EASEE® Lead will be fixed in place over

the pre-determined epileptic focus. Routine surgical planning or navigation systems may be used at the discretion of the Investigator.

First, a skin incision is made and the mobilized skin flap is folded away to reveal the periosteum. This layer is removed using standard surgical equipment, so that the surface of the skull becomes visible. At this point EASEE® Template is used to test the correct orientation and position of the electrode array. After this is established, the array itself is placed in the determined location. The cable part of the EASEE® Lead is then tunneled subcutaneously using the tunneling tool to the EASEE® Power implantation pocket via a retroauricular site. Once the tunelling has been completed, EASEE® Lead is srewed into place, starting with the central electrode. The peripheral electrodes are then attached one by one to the skull. Finally the strain relief is screwed onto the skull.

EASEE® Power is implanted in a procedure similar to other implantable pulse generators and may be implanted and secured in the implantation site before or after EASEE® Lead is implanted. After the cable has been connected to EASEE® Power, the surgical/neurological team will perform standard system diagnsotic testing using the hand-held programmer EASEE® Set and EASEE® Connect, to ensure that the system is functional. A representative of the Sponsor may be present during the operation to offer any technical support. Once the system diagnostic test is complete, EASEE® Power is sutured to the adjacent fascia and all the open wounds are closed.

Caution: Please refer to the Instructions for Use for a complete account of the implantation procedure.

9.5 Recovery

There will be a post-operative recovery period of 1 month to ensure that the healing processes can take place. The device will remain off during this period. A one-hour scalp EEG recording will be completed at the end of the recovery period and prior to configuration of the device.

9.6 Configuration

After the 1-month recovery period the device will be configured individually for each subject by the neurologist according to the EASEE® Stimulation Protocol and the stimulation will be turned on. All parameters with the exception of current amplitudes and ULFA starting time are predefined and not adjustable. The current amplitude should be configured individually for each subject and should be set at 0.1mA below the perception level. If the subject does not perceive the stimulation, then the current amplitude should be set to the maximum level i.e. 4mA. The ULFA starting time is recommended to be adjusted to 10 am. This timepoint may be changed at the discretion of the treating physician. Subjects should be observed for at least 30 minutes after the last stimulation adjustment to make certain that they are comfortable with the programmed stimulation pattern.

9.7 Evaluation Period

The evaluation period begins after configuration of the device at 1 month post-implant and lasts for a duration of 3 months. Stimulation will remain on during this time. At 4 months post-implant the primary safety endpoint will be analysed.

9.8 Follow-up Period

Once the evaluation period has been completed, the 12-month follow-up period will begin. AEDs should be kept constant during this time.

The stimulation parameters as defined in EASEE® Stimulation Protocol should be used until 8 months post-implant. At 8 months post-implant the Investigator will evaluate the benefit for the subject in agreement with the Sponsor:

- If it is deemed that the subject has benefited from the stimulation i.e. there is a reduction in the burden of epilepsy in terms of reduction in seizure frequency and/or severity, and/or improvement in QoL, neurocognition and the subject wishes to receive further stimulation, then the device may remain active up to the end of the follow-up period. If wished by the subject and at the discretion of the treating physician, one EASEE® Power replacement shall be provided by the Sponsor during this time in case of battery depletion.
- **I**f there has been no documented positive effect of stimulation, but the subject wishes to receive further stimulation, then the stimulation parameters may be changed at the discretion of the treating physician and in agreement with the Sponsor. If the subject does not wish further stimulation, then the device will be inactivated. If wished by the subject and at the discretion of the treating physician, one EASEE® Power replacement shall be provided by the Sponsor during this time in case of battery depletion.
- At any point during the study or after study completion all implanted components may be removed at the discretion of the physician and the patient.

There will be a safety visit at 12 months post-implant and the final visit will take place at 16 months post-implant. Other than the above visits, the subjects will not be required to visit the clinic more often than for their routine treatment.

9.9 Plan for Further Treatment

The implanted device will be disabled (turned off) in the following cases:

- the subject decides to no longer participate in the study ***or***
- the subject is excluded from study by the Investigator ***or***
- the study is aborted i.e. by Sponsor, Ethics Committee or Competent Authority ***or***
- the subject completes the study at the timepoint specified in the protocol (16 months post-implantation).

Therefore, in these cases no treatment (stimulation) will be delivered, other than that described in the study protocol up to this timepoint.

In case of battery depletion, EASEE® Power might require exchange or removal during the course of the study. It is recommended that EASEE® Power is removed at the end of the study. The risks associated with EASEE® Power removal or exchange are expected to be similar to those for implantation.

Removal of EASEE® Lead is not recommended, as the procedures associated with EASEE® Lead removal would pose an additional burden for the patient. EASEE® Lead will then remain in an inactive state, unless the patient enters a future study, such as a long-term follow-up study or the EASEE® System receives the CE Mark. In these cases, the implanted electrode will be reconnected to a newly implanted IPG and the stimulation may be reactivated.

At any point during the study or after study completion all implanted components may be removed at the discretion of the physician and the patient.

After the end of the study, the Principal Investigator will continue to follow up the patient with the implanted electrode on a regular basis and as per routine hospital practice.

The EASEE® System is not commercially available yet. Precisis AG, the Sponsor of the study, is currently in the process of receiving market approval in Europe in the next years. In case of any technical problem that might be encountered, the Investigator shall inform the Sponsor.

10 Statistical Considerations

10.1 General Statistical Considerations

This is a prospective, interventional, unblinded, multicenter study. The statistical population to be investigated is defined according to the intended use of the investigational device as well as the inclusion and exclusion criteria of the study. As a first in human study, the primary endpoints were chosen to be safety related and will assess probability of overall SAEs. Secondary endpoints are efficacy related and will assess probability of benefit to the patient.

10.2 Sample Size Calculation

Up to 15 subjects will be recruited. The primary goal of the study is to generate data regarding the feasibility and performance of neurostimulation with the EASEE® System. The results of this feasibility study will aid in the planning of a larger, sufficiently powered CE-Mark trial. Allowing for a conservative 20% dropout, there will be a minumum of 12 subjects available for analysis, which

meets the threshold for a sufficiently precise estimate of several factors to be used in future studies (Moore CG et al., 2011).

10.3 Study Population

The study population will consist of 15 adult subjects with medically refractory focal epilepsy, both males and females.

10.4 Demographic and Baseline Disease Characteristics

Demographic and disease baseline characteristics data collected will be summarized using descriptive statistics. Continuous assessments will be collated and summarized. In case of normal distribution of the data, mean and standard deviation willl be shown, otherwise standard boxplots will be used to present the data.

10.5 Statistical Methods

Normality of the data will be assessed visually using normality plots and, in addition, using a statistical test. Potential test with comparable test power are Anderson-Darling test, Shapiro-Wilk test or Jarque-Bera test.

10.6 Outcome Analysis

10.6.1 Primary Outcome

The following measures will be evaluated as part of the primary endpoint analysis:

- Incidence of acute SAEs: the number of subjects having a serious adverse event (SAE) for the surgical implant procedure and the following month, whether reported as device-related or not.
- Incidence of short-term chronic SAEs: the number of implanted subjects having a serious adverse event (SAE) for the surgical implant procedure and the following 4 months, whether reported as device-related or not.

The chosen maximum sample size that was based on experience from previous studies by other groups in the area of neurostimulation implants is 15 patients. Reliability of ‘No device failure’ is calculated based on the Binomial distribution. In case no SAE is found in the study reliability is 85% at a confidence level of 90% and 75% if one SAE is found in the study, respectively. In case of a conservative drop-out rate of 20%, only 12 patients would be available for analysis. In this case, reliability at 90% confidence level will drop to 81% for no SAE and 67% for one SAE during the study, respectively.

10.6.2 Secondary Outcomes

1. Seizure frequency: mean and median changes in seizure frequency compared to baseline and responder rate (defined as at least 50% reduction in seizure rate from baseline) at 4 months, 8 months and 16 months post-implant.
2. Seizure severity: baseline measurements of seizure severity compared to seizure severity data collected at 8 months and 16 months post-implant. Seizure severity will be evaluated using the SSQ scale (to be completed by the subject).
3. Epileptiform activity: scalp EEG data will be collected at baseline and at 1 month, 4 months, 8 months and 16 months post-implant. This data will be evaluated for typical surrogate markers of epileptic seizures e.g. spike and wave frequency.
4. Quality of life: subjects will complete the Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P) survey at baseline, 8 months and 16 months post-implant. The post-implant scores will be compared to baseline for each patient.
5. Mood: subjects will complete the Neurological Disorder Depression Inventory for Epilepsy (NDDI-E) survey at baseline, 8 months and 16 months post-implant. The post-implant scores will be compared to baseline for each patient.
6. Neurocognition: subjects will complete a battery of cognitive tests (for example EpiTrack®) at baseline, 8 months and 16 months post-implant. The post-implant scores will be compared to baseline for each patient.

For investigation of the obtained dataset, descriptive statistics will be performed by presenting frequency tables. In case of normal distribution of the data, mean and standard deviation may be shown, otherwise standard boxplots will be used to present the data. Afterwards, correlation analysis of the outcome parameter may performed using scatterplot matrices. Once a base set of measures describing the outcome of the study is found, statistical testing may be done to identify significant changes in the parameters from their baseline value. As this is a pilot study with a very small sample size, hypothesis testing will only be feasible in case of very high effect size which is not expected.

The following description is given as an exemplatory procedure for analysis of the data.Classical analysis of longitudinal data from one group of subjects at different time points is done using uni- or multivariate analysis of variance ((M)ANOVA) for parameter based analysis and i.e. Friedmann-test for non-parametrical testing, respectively. However, the test power of the latter is usually low and ANOVA is very specific regarding prerequisites of the data. Modern statistical analysis uses for example linear mixed effects models (LME, Galecki 2013). These regression based statistical models are very robust with respect to missing data or a lack in precision of the control variables and therefore often preferred over the classical approaches. The general model equation:

$$y = \mathbf{X}\beta + \mathbf{Zb} + \epsilon$$

thereby contains the response vector y with the measured parameter values, the known design matrix $\mathbf{X}$ describing the relationship between parameters and variables, the unknown fixed effects vector β, the known design matrix $\mathbf{Z}$ and the unknown vector of random effects $\mathbf{b}$. The results for

β of the maximum likelihood estimation may be tested for statistical significance using students t-test.

Afterwards, Pearson residuals r may be calculated from the errors $\epsilon_i = y_i - \mu_i$, using

$$r = \frac{\epsilon_i}{\sqrt{V(\mu_i)}}$$

with the measurements y_i, the corresponding predicted value μ_i, and the variance function $V(\mu_i)$. They can be used to assess model validity by analysis of normality and correlation. This is done visually using a normalized histogram of the residuals, a normalized quantile-quantile plot, a symmetry plot, a plot of residuals vs. their case number, a plot of residuals vs. the fitted values, and a lagged residual plot. If the model describes the effects of the treatment well, the errors between data and model should be random, resulting in a normal distribution of residuals with mean zero and no self-correlation.

10.6.3 Other Exploratory Analyses

Additional exploratory analyses may be conducted as deemed necessary. These analyses will be determined and described parallel to performing the statistical analyses.

10.7 Outcome Criteria

The outcome of this study will be assessed based on evaluation of the primary endpoint.

The following outcomes are possible:

- EASEE III study design is unchanged, if planned processes and design parameters are suitable
- EASEE III study design is adapted, if required and possible
- EASEE III study is cancelled, if the required changes are beyond available resources or if adverse event rates are classed as not acceptable.

11 Administrative Requirements

11.1 Sponsor Responsibilities

Precisis AG holds the overall responsibility for the conduct of this study including ensuring:

- Compliance with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.
- Protecting the rights, health, safety and welfare of study subjects.
- Informing the clinical Investigators of any new information about the study, which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.

- Providing the clinical Investigators with the study protocol and a full set of case report forms (CRF) on which to document the study evaluation variables for each subject entered into the study.
- Certifying that Ethics Committee (EC) approval of the study protocol and Investigator's Agreement will be completed prior to treatment at an investigational site.
- Compliance with EN ISO 14155.

11.1.1 Selection of Clinical Investigators and Sites

The Sponsor will select qualified Investigators according to the following criteria:

- Adequate study subject population to meet the requirements of the study
- Adequate time to be personally involved in the study
- Adequate research staff and resources to support the study
- Willingness to take the primary responsibility for the accuracy, legibility, and security of all study data
- Willingness to observe confidentiality at all times
- Willingness to follow protocol procedures and provide the Sponsor with accurate performance data in a timely fashion
- Associated with an Ethics Committee which satisfies all Competent Authority requirements and conducts meetings on a regular basis
- Access to appropriate medical facilities for pacing, defibrillation, and emergent cardiac surgery if needed
- Other requirements as previously noted in the study protocol

11.1.2 Training of Investigators and Site Personnel

The training of the Investigators and other clinical site personnel will be the responsibility of the Sponsor and/or designee and may be conducted during a site initiation visit, or other appropriate training sessions.

11.2 Investigator Responsibilities

The Investigator is responsible for the management of subjects involved in this clinical study as well as for the proper use of the investigational device at the study center. The Investigator will assume overall responsibility and accountability for the research team and for the clinical data obtained from subjects participating in the clinical study.

The responsibilities of the Investigator(s) comply with the requirements set forth in:

- The Declaration of Helsinki
- EN ISO 14155
- Local laws of the country – including the regulations of the European Union.

Additional responsibilities of the Investigator comprise:

- Ensuring that the clinical study is conducted according to the Clinical Investigational Plan (CIP).
- Obtaining informed consent on the approved Informed Consent Form prior to any study participation.
- Controlling any investigational device(s) stored at the site, if any. This includes supervising and disposal of devices and recording the receipt, disposition, and return of the investigational devices.
- Protecting the rights, safety and welfare of the subjects.
- Maintaining records and reports as listed in this Clinical Investigational Plan (CIP).
- Ensure full access to source documents for the study Monitor and regulatory agencies.
- Reviewing and signing all e-CRFs for subjects enrolled in the clinical study under the Investigator's care.
- Retaining records after completion of the study for a period determined by applicable local and national regulatory requirements.

11.3 Ethics Committee and Competent Authority

Documentation that the study has been approved by the respective Ethics Committee (EC) and Competent Authority (CA) must be present prior to study initiation. No changes will be made to study related documents (e.g. study protocol, informed consent form, etc.) without appropriate approvals, including Sponsor, EC and/or CA. Any amendments to the study protocol as well as associated informed consent form changes will be submitted to the EC/ CA and written approval obtained prior to implementation, according to local EC/ CA requirements. No investigative procedures other than those defined in this study protocol will be undertaken on enrolled subjects without the agreement of EC/ CA and Sponsor.

11.4 Informed Consent Process

A signed and dated informed consent form, as approved by the EC, shall be obtained from each subject prior to enrollment in the study. Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved Informed Consent Form. Once the Investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing and dating the Informed Consent Form. The Investigator shall also sign and date the Informed Consent Form and provide a copy to the subject. The original form shall be maintained at the investigational site. The informed consent process shall be documented in source document respectively.

11.5 Adverse Events

11.5.1 Definitions

- **Adverse event (AE)**: Any untoward medical occurrence , unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
  Note 1: This definition includes events related to the investigational medical device or the comparator.
  Note 2: This definition includes events related to the procedures involved.
  Note 3: For users or other persons, this definition is restricted to events related to the investigational medical devices.
- **Serious adverse event (SAE)**:
  Adverse event that
  a) led to death,
  b) led to serious deterioration in the health of the subject, that either resulted in
     1) a life-threatening illness or injury, or
     2) a permanent impairment of a body structure or a body function, or
     3) in-patient hospitalization or prolonged hospitalization, or
     4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  c) led to foetal distress, foetal death or a cogenital abnormality or birth defect.

  Note: Planned hospitalization for a pre-exisitng condition, or a procedure required by the CIP, without serious deterioraton in health, is not considered a serious adverse event.
- **Adverse device effect (ADE)**: adverse event related to the use of an investigational medical device
  Note 1: -this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
  Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device
- **Serious adverse device effect (SADE)**: adverse device effect that has resulted in any of the consequences characteristic of of a serious adverse event.
- **Unanticipated serious adverse device effect (USADE)**: serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
  Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
- **Device deficiency**: inadequacy of a medical device with respect to it´s identity, quality, durability, reliability, safety or performance.
  Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

11.5.2 Categorization of Adverse Events

Adverse events will be catogorized according to EN ISO 14155, Annex F.

11.5.3 Device Relationship

All adverse events will also be categorized by the Investigator as to device-relatedness and clinical ranking: mild, moderate, or significant according to the definitions below:

Mild	▪ Results in mild or transient discomfort, not requiring intervention or treatment. ▪ Does not limit or interfere with daily activities.
Moderate	▪ Results in sufficient discomfort so as to limit or interfere with daily activities. ▪ May require treatment.
Significant	▪ Results in significant symptoms that prevent normal daily activities. ▪ May require invasive intervention.

In addition, subjects will be instructed to contact the Investigator and/or study coordinator if any significant AEs occur between study evaluation visits. AEs will be collected throughout the entire course of the study.

The Investigator will use the following definitions to assess the relationship of the AE to the use of the investigational device:

Not Related	▪ Not associated with device application ▪ Due to an underlying or concurrent illness or effect of another device or drug
Unlikely	▪ Little or no temporal relationship to the study device **and/or** ▪ A more likely alternative etiology exists
Possible	▪ Temporal sequence between device application and event is such that the relationship is not unlikely **or** ▪ Subject's condition or concomitant therapy could have caused the AE
Probable	▪ Temporal sequence is relevant **or** ▪ Event abates upon device application completion/removal **or** ▪ Event cannot be reasonably explained by the subject's condition
Highly Probable	▪ Temporal sequence is relevant **and** ▪ Event abates upon device application completion/removal **or** event recurs on repeated device application

11.5.4 Safety Reporting to Sponsor and EC/CA

The Investigator will monitor the occurrence of adverse events for each subject after enrollment (at the time the subject has signed and dated the Informed Consent Form) and during the course of the clinical investigation. Adverse events (AEs) reported by the subject, observed by the Investigator or documented in medical records should be recorded on the adverse event e-CRF, whether believed by the Investigator to be related or unrelated to the investigational device. The Investigator will assess the nature, severity and device/procedure relationship of each AE. The site should report any new AE/experience that was not present at baseline, and/or worsening of a pre-exisiting condition (severity, frequency) compared to baseline. In case of a SAE and/or device deficiency, the Sponsor and/or designee must be notified immediately (within 24 hours of study staff awareness) by completing the designated forms in the e-CRF (*). All SAEs that result in death or are life threatening should be reported expedited. For the purposes of this study, seizures are considered a pre-existing condition and need only to be reported as AEs if they worsen (**) in severity or frequency during the study. The Sponsor and/or designee will take appropriate actions, according to EN ISO 14155 to report the SAEs and device deficiencies to involved lead ECs and CAs. The reporting must be performed according to the national requirements. In addition, the Sponsor and/or designee will submit, at least once a year for the duration of the clinical trial, a safety report to the involved ECs and CAs as required.

* **NOTE**:
AE reporting contact information hereafter may be used in lieu of reporting through the e-CRF, should the system be down:
genae safety group
Fax: +32 3 290 03 07
E-mail: easeeII@genae.com

****NOTE***:*
A worsening is defined as: a 100% increase in seizure frequency or increased seizure severity (aggravation of pre-existing seizures or occurrence of new seizure types) or the development of status epilepticus.

11.5.5 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be in place for the duration of the study and will review study data, among others for participant safety, study conduct and progress on a regular basis.

11.5.6 Early Termination of Clinical Trial

The Sponsor reserves the right to discontinue the clinical trial/investigation at any stage (e.g. for safety reasons) or reduce the follow-up period with suitable written notice to the Investigator.

Possible reason(s) include:

- Sponsor makes a final decision for the early termination of the clinical trial, or per DSMB recommendation
- Further product development is cancelled.

Should the clinical trial be discontinued by the Sponsor, subjects will be followed up as per routine hospital practice.

In this case, the Investigator shall return all clinical trial/investigation materials (including devices) to the Sponsor and provide a written statement as to why the premature termination has taken place to the EC (if applicable) and inform subjects still participating to the trial. All applicable Clinical Investigation documents shall be subject to the same retention policy as detailed in section 11.15 Record Retention. Sponsor or designee will inform the CA about premature termination of Clinical Trial as per regulatory requirements.

11.6 Monitoring Procedures and Responsibilities

In order to comply with clinical study regulations, to ensure the accuracy of the final study database, to ensure the overall quality and consistency of the study and to help Investigators, an employee of Precisis AG or designated CRO (Monitor) will visit each study site during the course of the study in order to review the study records and source documentation at site in accordance with the Monitoring Plan.

The responsibilities of the Monitor will include, but are not limited to:

- Comparing study data with any relevant source documents, such as medical records, questionnaires etc.,
- Checking the Informed Consent Form for each subject,
- Monitoring the general study records, including Investigator Site File, device traceability,
- Checking the occurrence of possible adverse events.

11.7 Study Initiation

Sites will be selected based on the feasibility process. The study must not be initiated until the Investigator has received written confirmation from the Sponsor that all pre-study documentation has been completed and necessary approval received. This includes documentation that the study site has concluded training on the study devices and study procedures.

11.8 Protocol Adherence

The study must be conducted, as set out in the study protocol, unless an emergency situation arises and immediate action is required that might deviate from the study protocol. Such deviations must be reported to the Sponsor and to the relevant EC. Protocol amendment is required for any non-emergency changes. This should be initiated by the Sponsor and must be approved by the involved

ECs. Depending on the impact of the change, supporting documents such as updated Informed Consent Forms must also be approved by the involved ECs. The approved and updated Informed consent forms must then be signed by each subject active in the study and by each new subjects, prior to proceeding with the study. The Investigator shall conduct no further studies/research other than that specified in the study protocol, without written approval from the Sponsor.

11.9 Protocol Deviations

It is the responsibility of the Investigator to ensure there are no deviations from the study protocol and that all actions are in full compliance with the EC. All protocol deviations shall be documented and a justification for any missed assessments or other non-compliance shall be provided on the Protocol Deviation Form in the e-CRF. The Investigator is required to sign this form on the appropriate pages to verify that she/he has reviewed and agrees with the recorded data. In the event of repeated non-compliance with the signed agreement, the study protocol or any other conditions of the study, the Sponsor may terminate the Investigator´s participation in the study.

11.10 Electronic Case Report Forms (e-CRFs)

All data that is to be collected according to the study protocol shall be reported into a validated electronic database (e-CRF) that has been provided by the Sponsor or designee. Edit checks will be implemented to ensure data quality and accuracy. The Sponsor or designee will also provide e- CRF completion guidelines, to ensure that the data is recorded in a timely and accurate manner. The Investigator is responsible for ensuring that all sections of e-CRF are complete and correct and that those entries can be verified against source data. Completed e-CRFs will be verified by the appointed Monitor at the investigational site at regular intervals throughout the study, as defined in the Monitoring Plan. All e-CRFs will be reviewed for completeness and clarity upon receipt. Missing or unclear data will be investigated by the Monitor and will be retrieved and clarified by study personnel as necessary throughout the study.

11.11 Source Documentation

Regulations and GCP require that the Investigator maintain information in the subject's medical records that corroborates the data collected in the e-CRF. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the study:

- Medical history of the subject before involvement in the trial sufficient to verify eligibility criteria
- Dated and signed notes on the day of entry into the trial referencing the Sponsor, protocol number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of relevant procedures and examinations)
- Adverse events reported and their resolution, including supporting documents such as discharge summaries, EEGs, and lab results including documentation of site awareness of

SAEs and of Investigator device relationship assessment of SAEs, death certificate or death confirmation (if applicable)

- Notes regarding prescription medication taken during the trial (including medication name, dose, frequency and duration as well as start and stop dates (day/month/year when possible)
- Subject's condition upon completion of or withdrawal from the trial
- Any other data required to substantiate data entered into the CRF

11.12 Source Document Review

The Investigator will allow the Monitor and/or the reprensentative of the Sponsor, and any regulatory body to review and inspect the study files, subject e- CRF, subject medical records and other related study documents as required. The Sponsor and/or designee may request additonal documentation from the Investigator such as physician procedure notes or physician written summaries when AEs are observed and reported.

11.13 Study Materials

11.13.1 Investigational Device Accountability

The Sponsor will provide investigational devices to each site, for which device accountability records must be maintained. All investigational devices, which have not been used must be returned to the Sponsor following completion of the study or as otherwise deemed necessary (e.g. expired devices).

Use of any investigational device supplied for use during this clinical trial outside of the study protocol (e.g. compassionate use) is strictly forbidden and may constitute grounds for removal of the Investigator/Institution from the clinical investigation. The Investigator will ensure no expired investigational devices are implanted.

All investigational devices that are associated with a device failure or device deficiency should be returned immediately to the Sponsor.

11.13.2 Other Study Materials

Unused subject binders may be destroyed at the end of the study; this should be documented. All other study materials should be returned to the Sponsor after the completion of the study.

11.14 Study Termination

The Sponsor reserves the right to terminate the entire study or a specific site's participation at any time for any of the following reasons: inadequate enrollment, protocol non-adherence, unethical practices, poor data quality or administrative decision.

11.15 Record Retention

The Investigators and/or designee(s) will be instructed to retain all study records required by the Sponsor and regulatory authorities in a secure and safe facility, with limited access. All study material shall be stored for at least 10 years or as based on national regulations. The Investigator must request authorization from the Sponsor prior to destroying study records.

11.16 On-site Audits

In the event that an Investigator is contacted by a regulatory agency in relation to this study, he/she shall notify the Sponsor and/or designee immediately. The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by authorized regulatory representatives during the audit process. The Investigator must provide the Sponsor and/or designee with copies of all correspondence that may affect the review of the current study or their qualification as an Investigator in studies conducted by the Sponsor and/or designee. The Sponsor and/or designee will provide any needed assistance to regulatory audits.

12 Labelling

All components will be labelled according to Directive 90/385/EEC, Annex 1, clause 14 and 15 and related harmonized standards. In addition, all devices used in the clinical trial will be clearly marked as “for clinical trial use only”. Draft labelling for the EASEE® System is included within the study package.

13 Sponsor Contact Information

The primary Precisis AG contact for the study is:
Dr. med. Angela Liedler
Hauptstr. 73
DE-69117 Heidelberg
Office: +49 6221 6559320
Fax: +49 6221 6559310
Email: a.liedler@precisis.de

14 Data Collection

14.1 Data Management Responsibilities

The handling of data, including data quality assurance, will comply with regulatory guidelines (for example GCP, EU- GDPR) and genae’s SOPs and work instructions. All steps and actions taken regarding data management and quality assurance will be documented in the genae’s SOPs and data handling guidelines. Completed e-CRFs will be verified against source data and visually

checked by the study monitor for completeness, consistency, and legibility. All adverse event terms recorded on the e-CRF will be entered into the sponsor's safety database. Responses to requests for further clarification of data recorded in the e-CRF will be answered, dated and signed by the Investigator. Changes will be implemented in the Sponsor's database and the data review and validation procedures will be repeated as needed. All AE information and textual comments will be proofread for consistency between the database and the e-CRF; the database will be corrected appropriately. At the end of the study, the database will be locked and the data will be released for reporting and statistical evaluation.

14.2 Confidentiality

The Investigator and institution involved in this study will only provide direct access to source data and documents to the Sponsor and/or designee, and to appropriate authorities for the purposes of monitoring, audit, EC review or regulatory inspection. Each subject taking part in the study will have agreed explicitly to such access in writing. All subject data will always be treated with strict adherence to professional standards of confidentiality and according to EU GDPR guidelines effective as of 25- May- 2018. All reports and communications relating to subjects in the study will identify the subjects by their subject ID number only.

15 Liability

Study subject insurance will be provided according to the laws of the respective country where the study will be conducted.

16 Publication Policy

The study will be registered in a Primary Registry of the WHO Registry Network. Registration will be the responsibility of the Sponsor and/or designee. Preparation of the publication will occur once the study has been concluded, but the Sponsor may at its discretion coordinate an additional, interim publication. The order of authorship will be determined by the Sponsor and will be in part based on the number of qualified and completing subjects at each site. The data and results from the clinical study are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. An Investigator may only publish data generated by this clinical study in accordance with the terms of the Clinical Trial Agreement.

17 Glossary and Abbreviations

AC	Alternating Current
AE	Adverse Event
ADE	Adverse Device Effect

AED	Antiepileptic Drug
e-CRF	Electronical Case Report Form
DBS	Deep Brain Stimulation
DSMB	Data Safety Monitoring Board
DC	Direct Current
CA	Competent Authority
CRO	Clinical Research Organisation
EASEE®	Epicranial Application of Stimulating Electrodes for Epilepsy
EASEE II	Feasibility study for the EASEE® System
EASEE® Access	A device that enables the subject to communicate with the implanted components
EASEE® Connect	A device that provides a wireless connection between EASEE® Set and EASEE® Power, enabling the input and extraction of data
EASEE® Lead	Part of the implant consisiting of the electrode and the cable
EASEE® Power	Part of the implant which stores energy and generates electrical pulses for stimulation
EASEE® Set	A physician control device to set parameters and manage the EASEE® Power
EASEE® System	The complete stimulation system consisting of the implant, the tools for the surgery, and management and maintenance tools for the implant
EC	Ethics Committee
EEG	Electroencephalogram
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
Hz	Hertz
ICH	International Conference on Harmonization
mA	Milliampere
MEDDEV	Guidance for the application of the classification rules for medical devices
min	Minutes
mm	Millimeter
MPSV	Medizinproduktesicherheitsverordnung - Medical Products Safety Ordinance
MRI	Magnetic Resonance Imaging
NDDI-E	Neurological Disorder Depression Inventory – Epilepsy scale
NHS3	The National Hospital Seizure Severity Scale
PI	Principal Investigator
QOLIE-E	Quality of Life in Epilepsy Inventory
RNS	Responsive Neurostimulation
s / sec	second
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect

SANTE	Stimulation of the Anterior Nuclei of Thalamus for Epilepsy
SSQ	Seizure Severity Questionnaire
SUDEP	Sudden Unexpected Death in Epilepsy
tDCS	Transcranial Direct Current Stimulation
ULFA	Ultra Low Frequency Asymmetric (stimulation mode)
USADE	Unanticipated Serious Adverse Device Effect
V	Volt
VNS	Vagus Nerve Stimulation
WHO	World Health Organisation
WMO	The Medical Research Involving Human Subjects Act

18 References

Assenza G, et al. (2016) Cathodal transcranial direct current stimulation reduces seizure frequency in adults with drug-resistant temporal lobe epilepsy: A sham controlled study. *Brain Stimulation* http://dx.doi.org/10.1016/j.brs.2016.12.005

Auvichayapat N, Rotenberg A, Gersner R, Ngodklang S, Tiamkao S, Tassaneeyakul W, Auvichayapat P (2013)Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy.*Brain Stimul*. Jul; 6(4):696-700.

Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, Srinivasan S, Jobst B, Gross RE, Shields DC, Barkley G, Salanova V, Olejniczak P, Cole A, Cash SS, Noe K, Wharen R, Worrell G, Murro AM, Edwards J, Duchowny M, Spencer D, Smith M, Geller E, Gwinn R, Skidmore C, Eisenschenk S, Berg M, Heck C, Van Ness P, Fountain N, Rutecki P, Massey A, O'Donovan C, Labar D, Duckrow RB, Hirsch LJ, Courtney T, Sun FT, Seale CG (2015) Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology*. Feb 24; 84(8):810-7.

Brodie MJ, Barry SJ, Bamagous GA, et al. (2012) Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 78:1548-54.

Chambers A, Bowen JM (2013) Electrical stimulation for drug-resistant epilepsy: an evidence-based analysis. *Ont Health Technol Assess Ser*. Oct 1;13(18):1-37.

Eddy CM, Rickards HE and Cavanna AE (2011) The cognitive impact of antiepileptic drugs. *Ther Adv Neurol Disord* 4(6): 385–407.

Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, Handforth A, Stern J, DeSalles A, Chung S, Shetter A, Bergen D, Bakay R, Henderson J, French J, Baltuch G, Rosenfeld W, Youkilis A, Marks W, Garcia P, Barbaro N, Fountain N, Bazil C, Goodman R, McKhann G, Babu Krishnamurthy K, Papavassiliou S, Epstein C,

Pollard J, Tonder L, Grebin J, Coffey R, Graves N; SANTE Study Group (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. May;51(5):899-908.

Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A (2006) A controlled trial of cathodal DC polarization in patients with refractory epilepsy. *Epilepsia.* 47(2): 335-342.

Ghani S, Vilensky J, Turner B, Tubbs RS, Loukas M. (2015) Meta-analysis of vagus nerve stimulation treatment for epilepsy: correlation between device setting parameters and acute response. *Childs Nerv Syst.* Dec;31(12):2291-304.

Greenberg MS. Handbook of Neurosurgery. Eigth Edition. *Thieme Medical Publishers, Inc.*, 2016. Part VIII, chapter 26: seizure, p: 440-460; part XXIII, chapter 100:seizure surgery: p. 1553-1559.

Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, Salanova V, Cole AJ, Smith MC, Gwinn RP, Skidmore C, Van Ness PC, Bergey GK, Park YD, Miller I, Geller E, Rutecki PA, Zimmerman R, Spencer DC, Goldman A, Edwards JC, Leiphart JW, Wharen RE, Fessler J, Fountain NB, Worrell GA, Gross RE, Eisenschenk S, Duckrow RB, Hirsch LJ, Bazil C, O'Donovan CA, Sun FT, Courtney TA, Seale CG, Morrell MJ (2014) Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia*. Mar; 55 (3):432-41.

EN ISO 14155. Clinical investigation of medical devices for human subjects -- Good clinical practice.

Kang JY, Wu C, Tracy J, Lorenzo M, Evans J, Nei M, Skidmore C, Mintzer S, Sharan AD, Sperling MR. Karvigh SA, Motamedi M, Arzani M, Roshan JHN (2017) HD-tDCS in refractory lateral frontal lobe epilepsy patients. *Seizure*. 47: 74-80.

Klinkenberg S, van den Bosch CN, Majoie HJ, Aalbers MW, Leenen L, Hendriksen J, Cornips EM, Rijkers K, Vles JS, Aldenkamp AP (2013) Behavioural and cognitive effects during vagus nerve stimulation in children with intractable epilepsy - a randomized controlled trial. *Eur J Paediatr Neurol.* Jan;17(1):82-90.

Larkin M, Meyer RM, Szuflita NS, Severson MA, Levine ZT (2016) Post-Traumatic, Drug-Resistant Epilepsy and Review of Seizure Control Outcomes from Blinded, Randomized Controlled Trials of Brain Stimulation Treatments for Drug-Resistant Epilepsy. *Cureus.* Aug 22;8(8):e744.

Lee KJ, Shon YM, Cho CB (2012) Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. *Stereotact Funct Neurosurg*. 90(6):379-85.

Longmore M, Wilkinson IB, Baldwin A, Wallin E. Oxford Handbook of Clinical Medicine. Ninth edition. *Oxford University Press*, 2014. Chapter: Neurology, p: 494-497.

Loring DW, Kapur R, Meador KJ, Morrell MJ (2015) Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia.* Nov; 56(11):1836-44.

Moore CG, Carter RE, Nietert PJ, Stewart PW (2011) Recommendations for planning pilot studies in clinical and translational research. *Clin Transl Sci.* Oct;4(5):332-7.

Panebianco M, Rigby A, Weston J, Marson AG (2015) Vagus nerve stimulation for partial seizures. *Cochrane Database Syst Rev.* Apr 3;(4):CD002896.

Ryvlin P, Gilliam FG, Nguyen DK, Colicchio G, Iudice A, Tinuper P, Zamponi N, Aguglia U, Wagner L, Minotti L, Stefan H, Boon P, Sadler M, Benna P, Raman P, Perucca E (2014) The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. *Epilepsia*. Jun;55(6):893-900.

Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, Labar D, Sperling MR, Sharan A, Sandok E, Handforth A, Stern JM, Chung S, Henderson JM, French J, Baltuch G, Rosenfeld WE, Garcia P, Barbaro NM, Fountain NB, Elias WJ, Goodman RR, Pollard JR, Tröster AI, Irwin CP, Lambrecht K, Graves N, Fisher R; SANTE Study Group. (2015) Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*. Mar 10;84(10):1017-25.

San-Juan D, López DAE, Gregorio RV, Trenado C, Aragón MFG, Morales-Quezada L, Ruiz AH, Hernandez-Gonzalez F, Alcaraz-Guzman A, Anschel DJ, Fregni F (2017) Transcranial direct current stimulation in mesial temporal lobe epilepsy and hippocampal sclerosis. *Brain Stimulation.* 10(1), 28-35.

Sohal VS, Sun FT (2011). Responsive neurostimulation suppresses synchronized cortical rhythms in patients with epilepsy. *Neurosurg Clin N Am*. Oct;22(4):481-8.

Sprengers M, Vonck K, Carrette E, Marson AG, Boon P (2014) Deep brain and cortical stimulation for epilepsy. *Cochrane Database Syst Rev.* Jun 17;(6):CD008497.

Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M, Kasper BS,Hammen T, Rzonsa M, Pauli E, Ellrich J, Graf W, Hopfengärtner R (2012) Transcutaneousvagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. *Epilepsia*. Jul;53 (7):e115-8.

Varga ET, Terney D, Atkins MD, Nikanorova M, Jeppesen DS, Uldall P, Hjalgrim H, Beniczky S (2011) Transcranial direct current stimulation in refractory continuous spikes and waves during slow sleep: a controlled study. *Epilepsy Res.* Nov;97(1-2):142-5.