***Electrical Stimulation of Thalamus for Epilepsy of Lennox-Gastaut Phenotype***

***(ESTEL)***

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**ESTEL Protocol - Contents**

1. Summary
2. Introduction

2.1 Lennox-Gastaut Syndrome (LGS)

2.2 Rationale for thalamic stimulation

2.3 Centromedian Nucleus Stimulation

1. Study Objectives

3.1 Hypothesis

3.2 Outcome measures

3.2.1 Primary outcome measure (efficacy)

3.2.2 Secondary outcome measures (efficacy)

3.2.3 Secondary outcome measures (safety)

3.2.4 Exploratory outcome measures

1. Study Design

4.1 Study description

4.2 Study variables

4.2.1 Seizure frequency

4.2.2 Burden of epileptic activity

4.2.3 Global assessment of severity of epilepsy (GASE)

4.2.4 Global assessment of disability (GADS)

4.2.5 Cognitive functioning

4.2.6 Quality of life (QOLIE-31) and Depression (PHQ-9)

4.3 Study setting

4.3.1 Baseline, pre- and post-implantation assessments

4.3.2 Implantation of electrodes and stimulator

4.3.3 Statistical image analysis

4.3.4 Team

4.4 Schedule of assessments – Table 1

4.5 Participants

4.5.1 Inclusion criteria

4.5.2 Exclusion criteria

1. Study Treatment

5.1 Neurostimulator and electrodes

5.2 Stimulation

5.3 Blinding

5.4 Pre-implantation imaging

5.4.1 Anatomical

5.4.2 Functional (EEG-fMRI)

5.5 Randomisation

5.6 Epilepsy medications

1. Assessment of Efficacy

6.1 Outcome

6.2 Sample size

1. Safety

7.1 Implantation

7.2 Stimulation

7.3 Visits/time/inconvenience

7.4 Ionising Radiation

7.5 Definition of Adverse Events

7.6 Safety monitoring

7.7 Battery Life

1. Budget

***Electrical Stimulation of Thalamus for Epilepsy of Lennox-Gastaut Phenotype (ESTEL)***

**1. Summary**

Of the 1 in 200 Australians with epilepsy, 30% continue to have seizures despite anti-epileptic medications (1). Around 5% benefit from epilepsy surgery to remove an epileptic focus, but there is a significant proportion of patients with epilepsy in whom resective surgery is either not an option or has been unsuccessful. Deep brain stimulation (DBS) has recently been approved for treatment of epilepsy in Australia, based on the SANTE study, offering a new treatment option for patients with focal epilepsy (2). The role of DBS in generalised epilepsy is currently unclear.

5% of patients with epilepsy, including a significant proportion of those with medication resistant epilepsy, have Lennox-Gastaut Syndrome (LGS), a severe generalised epilepsy syndrome (3). EEG (electroencephalography) shows characteristic generalised epileptic activity that reflects recruitment of distributed cerebral networks (4). The condition typically begins in young children, leaving many with recurring seizures throughout their adult life (5). Some patients have to wear a helmet to reduce head and face injuries from daily seizures. Ongoing seizures significantly add to patient dependency and carer burden. There is a clear need for new treatment approaches in this severely affected group.

In this study we evaluate Deep Brain Stimulation to the thalamus as a treatment for Lennox-Gastaut Syndrome, in a randomised, double blind, placebo controlled trial.

**2. Introduction**

**2.1 Lennox-Gastaut syndrome (LGS) -** is a severe generalized epilepsy syndrome associated with recurrent epileptic seizures, generalised epileptic discharges and intellectual disability (6). The underlying cause is often unknown, although individual patients may have a variety of genetic abnormalities or cortical lesions. The electroclinical features of LGS are remarkably similar whether or not there is a causative lesion or gene, consistent with the notion that LGS is an expression of shared mode of epileptic brain behavior (4). Onset of LGS is before the age of eight years in 90% (3), and once established 80% of LGS patients will continue to have seizures into adulthood. This results in LGS having a relatively high prevalence of ~5% people with epilepsy (7). Anti-convulsants are often ineffective, leaving patients with daily seizures, and frequent hospital presentations.

Tonic seizures, which cause patients to suddenly and unpredictably stiffen and drop to the ground, are a prominent and dangerous clinical feature (8). On EEG (electroencephalography), tonic seizures are characterised by a diffuse high voltage slow wave followed by generalised low voltage fast activity reflecting sustained fast neuronal firing over a wide cortical area. The EEG between seizures is very active, with frequent runs of pseudo-rhythmic 1.5–2.5 Hz diffuse slow spike-and-wave (SSW), and intermittent bursts of generalised paroxysmal fast activity (PFA), particularly in sleep (3).

LGS is classified as one of the epileptic encephalopathies (6), as it seems likely that the epileptic process pervasively inhibits cognition and cognitive development. Children with LGS frequently show cognitive regression around the time of diagnosis, whilst established LGS is almost always associated with at least moderate cognitive impairment (3, 9). An earlier age of seizure onset (<5 years) has been associated with more severe cognitive impairment, while patients who develop LGS later in life (>9 years) follow a more favourable cognitive course. Behavioural and psychiatric disturbances are frequent in LGS, compounding the burden of care.

Ongoing epileptic activity probably continues to contribute to cognitive impairment. In patients with poorly controlled seizures, there appears to be progressive cognitive decline, with one study finding a drop of 15 IQ points over 17 years of follow-up (10). In contrast, there are a number of case reports of improved cognitive trajectory in patients with LGS due to a lesion, who become seizure free following resective surgery (12). Hence, ongoing epileptic activity may continue to impede cognition, and effectively treating this may prevent further cognitive decline. The earlier epileptic activity can be suppressed, the greater than chance for cognitive recovery.

Our landmark studies have suggested LGS is a cognitive network epilepsy, where epileptic discharges and seizures reflect abnormal neuronal firing within intrinsic cognitive networks (figure 1). Our functional neuroimaging studies have revealed that the epileptic activity of LGS recruits widespread areas of association cortex, containing key cognitive networks, but spares primary cortical regions (11, 13, 14). Epileptic activity appears ‘generalised’ on EEG because these cognitive networks are widely distributed. We find it useful to conceptualise LGS as a ‘secondary’ cognitive network epilepsy (4), because epileptic discharges and seizures reflect epileptic activity that has been amplified through intrinsic cognitive brain networks, rather than reflecting the specific lesional, genetic, or other cause.



**Figure 1:*****EEG-fMRI group activation maps for the epileptic discharges of LGS:***

*Generalised Paroxysmal Fast Activity (PFA, top), Slow Spike and Wave (SSW, bottom), EEG examples on left; p<0.05 corrected, activation=red, deactivation=blue. GPFA shows diffuse association cortex activation. SSW shows a more complex pattern.*

*Both PFA and SSW show activation of the thalamus.*

*(Archer et al, Epilepsia 2014) (7)*

**2.2 Rationale for thalamic stimulation** **-** The generalised nature of epileptic discharges and seizures has led many to postulate that thalamic involvement is integral to the epileptic activity of LGS. This may be as a synchroniser and amplifier of the epileptic network. Depth electrode recordings from the thalamus during generalised epileptic discharges of LGS have shown sustained burst firing in the centromedian nucleus during the low voltage fast activity that occurs at the start of tonic seizures. (15, 16). EEG-fMRI studies have shown thalamic involvement during slow spike-and-wave (13, 17) and generalised PFA (11) (see Fig 1).

After several smaller studies indicated potential benefit of thalamic stimulation for epilepsy (18), the SANTE study of DBS to bilateral Anterior Nucleus of Thalamus (AnT) provided class 1 evidence for a reduction in seizures of 30-50% in patients with partial onset seizures (2). In particular, of 110 patients with partial onset seizures treated with DBS-AnT in the SANTE study, 54% showed a 50% reduction of seizures by 2 years. An open label extension phase suggests there may be progressive benefit, with seizure rates falling to 70% of pre-implantation levels by 5 years, and 16% achieving more than six months of seizure freedom (19). The SANTE study used continuous, cycling stimulation; 5 volt, 90µsec stimulation pulses, 145 pulses/second, ‘‘ON’’ 1 min, alternating with ‘‘OFF’’ 5 min. AnT was chosen as the target in the SANTE study because a large proportion of patients with focal epilepsy have seizures arising from the frontal or temporal lobes, cortical regions that have strong projections from AnT. There have been no AnT stimulation studies in LGS cohorts.

The overall safety of deep brain stimulation has been established through many years of experience in movement disorders, showing a low risk of complications. In the SANTE trial there were no clinically significant haemorrhages, but there was a 10% risk of infection that is consistent with movement disorder series, 2/3 requiring removal of the device. Issues specific to anterior thalamic stimulation were an initial 15% risk of reported depression, and a 13% risk of subjective memory disturbance, likely reflecting the projections of this nucleus to the limbic system. These neuropsychiatric symptoms were not apparent on formal testing, and appeared to abate with time. By one year, a majority of patients reported improvements in cognition compared to pre-implantation, confirmed on formal testing of attention and executive function, with this benefit being sustained at 5 years (19).

**2.3 Centromedian Nucleus Stimulation -** The centromedian nucleus (CM) of the thalamus can modulate excitability across widespread cortical regions. CM receives inputs from the cerebral cortex (including motor and pre-motor cortex), spinothalamic tract and various brainstem regions including the pontine reticular formation. CM projects widely to the cortex via polysynaptic projections, as revealed by autoradiographic labeling studies in cats, showing projections diffusely to layer 1 of the cortex, in turn regulating cortical output from deeper layers. CM also projects to basal ganglia, hypothalamus, and other thalamic nuclei (20). 5-12 Hz stimulation of CM in cats elicits a ‘recruiting response’ over wide areas of association cortex, characterized by time locked waveforms that build in amplitude over successive stimulations (21), suggesting that CM has the ability to modify excitability diffusely over the cortex. Low frequency 2 Hz stimulation of CM in a human subject with electrodes implanted chronically for epilepsy, invoked widespread changes in cortical activation, including diffusely over mesial and lateral frontal and parietal cortices (22).

Unblinded studies of continuous CM stimulation have been promising, with dramatic reductions in generalised seizures following implantation and stimulation (23). A non-controlled study of CN-DBS in 13 LGS patients reported an 80% reduction in seizures (24), although a subsequent small, placebo-controlled study of CN stimulation (only 2 hours ‘on’ per day) showed wide variability in response between subjects, and overall a non-significant 20% benefit (25). A recent blinded but uncontrolled study of CM stimulation for generalised epilepsy also reported an 80% reduction in seizures in the two subjects with LGS, including substantial initial benefit from the implantation alone, even prior to switching on stimulation (26).

Minimal side effects of centromedian nucleus stimulation have been reported in the epilepsy studies to date, although neuropsychologic data has not been systematically collected (24, 26). CM stimulation has also been trialed for reduction of tics in Tourette’ syndrome. One study in six Tourette’s patients, showed that stimulated patients needed more time to complete the Stroop colour-word task, an assessment of frontal lobe function. The significance of this finding to patients with LGS is uncertain, given pre-existing cognitive dysfunction.

In summary, there is modest evidence from several uncontrolled studies that CM stimulation is likely to be beneficial in reducing seizures in LGS. The neurocognitive side-effect profile of CM stimulation needs more careful characterisation, but stimulation appears unlikely to be associated with major deficits, should be reversible upon switching off stimulation, and based on experience with stimulation in AnT, induced changes in cognition are likely to gradually normalize with time.

**3. Study Objectives:**

The overall aim of this study is to show that electrical deep brain stimulation of the centromedian nucleus of the thalamus is a safe and effective treatment for patients with Lennox-Gastaut Syndrome.

**3.1 Hypothesis:**

*Continuous, cycling stimulation to the centromedian nucleus will reduce seizures in patients with Lennox-Gastaut Syndrome, compared to patients not receiving stimulation.*

**3.2 Outcome measures:**

3.2.1 – Primary outcome measure (efficacy)

1) *Proportion of participants with a 50% or greater reduction in seizures, will be higher in the stimulated group compared to those not receiving stimulation, measured after three months of stimulation.*

3.2.2 – Secondary outcome measures (efficacy)

2a) Monthly total seizure frequency, estimated from seizure diaries, will be reduced in subjects receiving CM stimulation, compared to their seizure frequency prior to stimulation.

2b) Global assessments of epilepsy severity, measured after three months of stimulation, will be improved in subjects receiving CM stimulation.

2c) The burden of epileptic activity (bursts of generalized paroxysmal fast activity per hour), will be reduced in subjects receiving CM stimulation.

3.2.3 - Secondary outcome measures (safety)

2d) Seizure frequency will not increase in subjects receiving CM stimulation.

2e) Cognitive functioning (Adaptive Behaviour Assessment System – ABAS-II) will not deteriorate in subjects receiving CM stimulation.

2f) Global assessments of disability, measured after three months of stimulation, will not deteriorate in subjects receiving CM stimulation.

3.2.4 – Exploratory outcome measures

3a) Reductions in the rate of epileptic discharges on EEG (bursts of generalized paroxysmal fast activity per hour) will correlate with reductions in monthly seizure frequency.

3b) Pre-implantation functional MRI involvement of CM during epileptic discharges will predict response to subsequent CM stimulation.

**4. Study Design**

4.1 Study Description - Prospective, randomised, double blind, study of continuous, cycling stimulation to bilateral CM, utilising a parallel group design. Because effect size is unknown, we will use an adaptive sample size re-estimation according to the promising zone method after the outcomes of the first 20 subjects have been observed (27). This study design mimics many of the features of SANTE, but examines treatment effect in a different patient cohort (Lennox-Gastaut Syndrome). Subjects are selected according to inclusion and exclusion criteria listed below, then entered into a three-month baseline observation phase, prior to implantation. Following implantation there is a three-month phase of observation, before half the subjects (n=10) have stimulators turned on (blinded). Both active (stimulator on) and control (stimulator off) groups are monitored for the next three months. The Primary outcome measure (seizure frequency measured over four weeks) will be obtained from this blinded controlled phase of the study. On completion of the blinded phase, the remaining half of subjects (n=10) have stimulators turned on. Both groups are then monitored for a further three months (month 12 from recruitment, month 9 from implantation, month 3 or 6 from stimulation on). Secondary outcome measures will be obtained from this observation phase.

4.2 Study Variables –

4.2.1 *Seizure frequency* – measured from a seizure diary, in which subjects and/or carers record events daily. Seizure counts are totalled over a (28 day) month to determine monthly seizure frequency

4.2.2 *Burden of epileptic activity* – 24 hour ambulatory EEG recorded pre-implantation, three months post-implantation but pre-stimulation, three months post stimulation and at the end of the study. Bursts of epileptic activity (generalised paroxysmal fast activity) are identified by a combination of automated computer detection and manual confirmation. The rate of discharges per hour is calculated.

4.2.3 *Global assessment of severity of epilepsy* (GASE) – a validated 7 point rating scale (28),(29), that assesses the overall current severity of epilepsy.

4.2.4 *Global Assessment of Disability* (GADS) - a validated 7 point rating scale (30), that assesses the current impact of epilepsy on the patient’s life.

4.2.5 *Cognitive functioning* - assessed using the computerized NIH Toolbox, Adaptive Behaviour Assessment System – Third Edition (ABAS-3) (31), which measures skills in 10 areas including communication, self direction, home living, and self care. To estimate each subject’s general intellectual function (Full Scale IQ), we use the Australian-normed, age appropriate version of the gold standard Wechsler Intelligence Scales, which provide robust age-scaled indices and scores for verbal and nonverbal cognitive abilities, attention and working memory function and processing speed.

4.2.6 *Quality of life* (QOLIE-31) and *Depression* (PHQ-9) – these questionnaires, which have been validated in epilepsy populations (32, 33), will be performed in those patients whose intellectual function allows meaningful completion.

4.3 Study Setting -

4.3.1 Baseline, pre- and post-implantation assessments:

* 1. Clinical assessments (outpatient): Melbourne Brain Centre, University of Melbourne, Austin Health
  2. Ambulatory EEG (outpatient): attachment / disconnection – EEG laboratory 6N; EEG signal analysis – Melbourne Brain Centre (University of Melbourne)
  3. Neuropsychology / cognitive assessments (outpatient): Melbourne Brain Centre, and Austin Health.
     1. Implantation of electrodes and stimulator:
  4. Operation - Neurosurgery theatre Austin Health
  5. Immediate post-op care – Neurosurgery ward Austin Health
     1. Statistical and image analysis: Melbourne Brain Centre, University of Melbourne, Austin Health

4.3.4 Team: We have brought together a unique team that combines clinical and research expertise in epilepsy and DBS. Dr Archer’s imaging studies in Lennox-Gastaut Syndrome have led to major new insights into the mechanisms underlying this devastating condition. Dr Thevathasan and Mr Bulluss have been instrumental in establishing the Parkinson’s DBS program at Austin Health.

4.4 Schedule of assessments - See table 1 for timing schedule of assessments. Clinical assessments are performed by a clinician blinded to whether the patient is in the active stimulation, or observation arm. Subjects will be seen monthly once implanted until completion of the study, with an additional two visits for one real (2.5V => 5V) and one sham stimulator adjustment.

After recruitment, total number of visits is: 1 (baseline; wk -12); 2+*1* (surgery + post-implant monitoring; wk 0, 4) *[+wk 8 via telephone]*; 3+*1* (post (sham-) stimulation; wk 12, 14, 16) *[+wk 20 via telephone]*; 3+*1* (post (sham-) stimulation; wk 24, 26, 28) *[+wk 32 via telephone]*, 1 (exit; wk 36). In total there will be 10 direct contact visits, and 3 telephone contacts.

4.5 Participants - Initial phase 20 subjects. Subjects must have had previous assessment in a comprehensive epilepsy unit, including an EEG consistent with the diagnosis of Lennox-Gastaut Syndrome, and an epilepsy directed MRI-B to exclude a surgically amenable lesion.

4.5.1 *- Inclusion criteria:*

1. Aged between 15-65 years
2. Electro-clinical diagnosis of LGS, as defined by: a) generalized paroxysmal fast activity (PFA) and slow spike and wave (SSW) on EEG, and b) tonic seizures documented on prior video-EEG monitoring or clearly described by a reliable eye-witness.
3. Seizure frequency (tonic seizures and/or convulsions) ≥ 4 per month (28 days) - atypical absence can be present, but are not an inclusion criteria as these seizures are too difficult to reliably document.
4. Stable dose of > 2 concomitant anti epileptic drugs (AEDs).
5. Previously failed at least 3 prior AEDs. Prior VNS or neurosurgery is permitted.
6. Amenable to frequent hospital visits.
7. Able to accurately self-report seizures, or consistent and reliable carer who can maintain an accurate seizure diary.

4.5.2 *- Exclusion criteria:*

1. Predominant seizure type is focal dyscognitive seizures (complex partial seizures).
2. Residents of a group environment with rotating or non-consistent carer*.*
3. Participants unable to comply with stable AED doses for >40 weeks.

**5. Study Treatment**

5.1 Neurostimulator and electrodes - Medtronic Model 3387 or 3389 DBS leads (Medtronic, Minneapolis, MN, U.S.A.), connected to a dual-channel Active PC neurostimulator via low profile extension connectors will be tunneled subcutaneously. DBS electrodes are implanted in the CM bilaterally under general anesthetic using a framed-based stereotactic technique, aided by intraoperative electrophysiology recordings. A CT brain is performed after the frame is in place to enable accurate reference of the brain in 3D space (*“frame space = brain space”*). The trajectory typically runs from an entry point at the coronal suture at an angle around 5-15 degrees lateral from the mid-sagittal plane. The CM target is directly identified lateral to the internal thalamic lamina (see figure 2). Once the brain electrodes are in place, intraoperative recordings from the CM and scalp evoked potentials are recorded, to confirm electrode location. Intraoperative skull X-rays (approximately 8 [4 each hemisphere]) and short periods of fluroscopy (approximately 10 seconds, [5 seconds each hemisphere]) performed using image intensification x-ray are also used to confirm electrode position. Electrodes are then connected to extension cables and the implantable pulse generator which are implanted fully subcutaneously. Positioning of the electrodes is further confirmed with a post-operative CT co-registered with the pre- operative MRI.

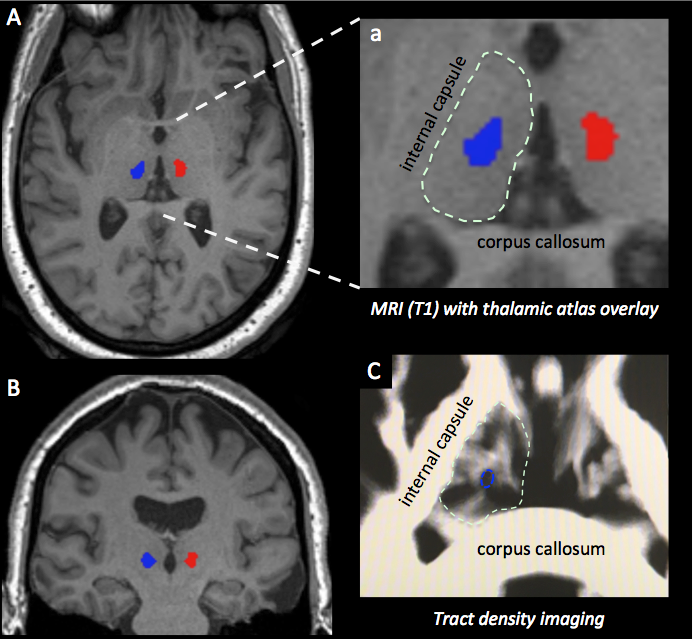
5.2 Stimulation - After implantation, all subjects will have seizures monitored monthly for three months to quantify the influence of the procedure alone (‘micro-lesion’ effect), which could confound the benefit of stimulation. After this three month observation period, 10 subjects (treatment) will have stimulators turned on; continuous, cycling stimulation, 90µsec stimulation pulses, 145 pulses/second, ‘‘ON’’ 1 min, alternating with ‘‘OFF’’ 5 min. Stimulation is initially turned on at 1.0V, and increased by after two weeks to the target of 2.5V, unless there are unexpected side effects. Voltages may be adjusted from these quoted depending upon participant tolerance. In all cases, these target voltages should be consisted as much as possible.

5.3 Blinding - Stimulation is adjusted by a trial staff, with clinical assessments including monthly recording of seizures being made by a separate clinician (CI-Archer or proxy). Patients in the control group also have sham ‘stimulator adjustment’ visits. After the three month blinded phase, the remaining 10 subjects have stimulators turned on, following the titration schedule described above, whilst the initial 10 subjects will have ‘sham adjustment’.

5.4 Pre-implantation Imaging - performed at Melbourne Brain Centre Austin Health, or Austin radiology department:

*i) Anatomical:* To enhance accuracy of electrode placement we use direct targeting of CM determined from advanced pre-operative imaging, rather than co-ordinate based targeting as was used in SANTE. We acquire 3D T2 FLAIR sequence, high resolution SWI sequence (0.5 x 0.5 x 2mm) and 3D T1 MPRAGE pre and post-gadolinium sequences (34, 35, 36) and a 15 Free Run data acquisition with multiband sequence. The purpose is to define vascular anatomy adjacent to the thalamus and to locate the CM nucleus. We use a published thalamic atlas, derived from high resolution histologic sections (36), and coregistered into MRI space, allowing display of the location of CM on the patient’s own MRI (figure 2A, B). If time permits volumetric diffusion weighted sequences (b3000/60 directions), that allow us to construct tract density images (37), providing superior definition on internal thalamic architecture (38) and 3D MP2RAGE with fluid and white matter nulled (FLAWS) sequences will also be acquired. The *Lamina medullaris medialis* (internal thalamic lamina), which wraps around the CM nucleus, is a useful landmark (figure 2C).

*ii) Functional (EEG-fMRI):* Whole brain T2\* weighted fMRI images acquired using a multi-slice gradient-recalled echo-planar imaging (EPI) sequence. EEG is acquired continuously during imaging using commercial MR-compatible EEG system (BrainAmp MR, Munich). After fMRI pre-processing, the haemodynamic response to spiking is modelled using an event-related design (11).



**Figure 2:** *Pre-operative imaging on a recent epilepsy DBS patient. T1 weighted MRI (MPRAGE sequence); A-axial (expanded in a), B-coronal. C- tract density imaging (TDI) derived from diffusion weighted MRI. Dashed green line = outline of thalamus. Red and blue regions indicate location of CM nucleus based on thalamic atlas co-registered to individual patient’s MRI. TDI allows visualization of thalamic architecture for additional information on CM location (dashed blue oval).*

5.5 Randomisation – Participants will be randomized after completion of the three-month post-implantation observation phase, to receive either immediate stimulation (beginning at 3 months after the implantation) or delayed stimulation (beginning at 6 months after the implantation – control group) in the ratio 1:1 stratified by age (below vs above 30 years of age) (39). With one implantation per month, it will take approximately two years for all 20 subjects to be implanted.

5.6 Epilepsy Medications – Participants will be required to maintain stable doses of epilepsy medications over the duration of the study. Rescue doses of benzodiazepine medications are permitted.

**6. Assessment of Efficacy**

6.1 Outcome – The primary outcome is the proportion of responders (participants with 50% or greater reduction in seizures) in stimulated versus unstimulated groups. This will be tested using a logistic regression model, with an outcome being achieved (responder =1; non-responder =0), the input being the group (stimulated vs not stimulated), and the baseline seizure frequency as a treatment covariate for adjustment purposes. The effect sizes will be reported as odds ratios with 95% confidence intervals.

Secondary endpoints, comparing seizure frequency before and after implantation, and PFA rate before and after implantation, will be investigated using repeated measures random effect regression modelling, due to the longitudinal nature of the data. Safety endpoints will be investigated using appropriate binary or count outcome regression models depending on the nature of the outcome.

Exploratory endpoints, of association between hourly PFA rate and monthly seizure rate will be tested by a correlation analysis. Pre-implantation EEG-fMRI percent signal change in CM will be correlated against post-implantation percent seizure reduction.

6.2 Sample Size - Seizures are frequent in Lennox-Gastaut Phenotype, with most patients having attacks at least daily. In LGS patients previously implanted, seizure reduction is reported to be approximately 70%. The primary outcome is the proportion of responders (participants with 50% or greater reduction in seizures) in stimulated versus unstimulated groups. 10 patients per group will yield 80% power to detect a statistically significant difference of 60% or higher in proportions of responders (70% in stimulated, 10% non-stimulated), assuming an alpha of 0.05.

**7. Safety**

Adverse events related to the study can be broken down into surgical/device risks, stimulation risks, and risk/inconvenience related to pre- and post-operative assessments.

**7.1 Implantation:** Implanted neuro-stimulators are becoming increasingly used to treat a variety of neurologic disorders. However, there are some established risks related to the procedure. These include:

1. Haemorrhage: Due to piercing of blood vessels by the thalamic electrode. In SANTE there were no clinically significant haemorrhages, but 4.5% patients had micro-haemorrhage detected on post-op imaging, which did not require intervention. We perform pre-implantation contrast enhanced imaging to define arterial and venous structures surrounding the thalamus, and plan an electrode trajectory that avoids visible vessels. Our experience with DBS for Parkinson’s disease is a 1% risk of haemorrhage, half of these (0.5%) symptomatic.
2. Infection: With the introduction of any foreign body there is a risk of infection. In SANTE there was a 12% risk of infection; 7% at the stimulator pocket, 6% at the tunneled lead, 2% at the burr hole, with 2/3 requiring stimulator box or lead removal. Our center’s infection rate for DBS electrodes for Parkinson’s Disease is approximately 4-5%.
3. Lead repositioning: SANTE used an indirect, atlas based targeting, where co-ordinates are determined from a standardized atlas, and 8% subjects required lead repositioning after post-op imaging confirmed electrodes were not in AnT. We use direct targeting, based on high resolution MR imaging of the patient and intraoperative microelectrode recording (40), allowing us to visualize and account for patient specific variations in anatomy for improved accuracy (41). Our lead repositioning rate in Parkinson’s Disease is 2.5%.
4. Death: The risk of death following stereotactic neurosurgical procedures is approximately 0.01% (1 in 1000). In SANTE no patients died during implantation or the three month blinded phase, but 4 died during nine months of follow-up, including one drowning, one suicide, and two SUDEP (Sudden Unexplained Death in Epilepsy, presumed related to cardiorespiratory arrest during a seizure).
5. Pain: 11% patients in SANTE reported discomfort at the site of the stimulator box, although this did not necessitate removal.

**7.2 Stimulation:**

a) Parasthesiae (tingling): Stimulation is usually asymptomatic, with none of 13 patients receiving CM stimulation reporting side effects (24). There are isolated reports of patients with parasthesiae when CM stimulation was first switched on, possibly due to more lateral than intended placement of the electrode, and spread of stimulation to the adjacent VPL/VPM sensory relay nuclei of the thalamus.

b) Cognitive changes: In LGS patients studied so far, there do not appear to be adverse cognitive effects, and indeed some reports of improved ‘alertness’ (42). This may relate to suppression of recurrent epileptic discharges and seizures, allowing the subject’s cognitive potential to be released from a state of ‘epileptic encephalopathy’ (43). However we note that six patients receiving CM DBS for Tourette’s syndrome showed a deterioration in performance on the Stroop colour-word task, a test of frontal lobe function (44). Hence we are including a battery of neuropsychologic tests (specifically NIH Toolbox), to document any positive or negative cognitive changes with stimulation. ABAS-3 is a validated scale developed for use in individuals with a range of intellectual abilities, that measures functioning and behavior across a range of domains (31). GADS provides a global assessment of the degree of disability. PHQ-9 and QOLIE-31 will assess for depression in subjects capable of completing the questionnaires. Stimulation can be switched off if cognitive changes are considered unacceptable.

c) Seizure exacerbation: In SANTE, one patient (out of 110) had marked exacerbation of seizures when the stimulator was switched on, with multiple hourly attacks. The stimulator was switched off, with seizures ceasing, and later restarted at a lower voltage without exacerbating seizures. There are no reports of seizure exacerbation with CM stimulation. We are measuring seizure frequency (Primary Outcome), as well as a global impression of severity of epilepsy (GASE).

**7.3 Visits / time / inconvenience:**

This double-blind, placebo controlled study seeks to provide level 1 evidence for the safety and effectiveness of CM DBS for LGS. This requires careful documentation of seizure counts, adverse events, neurocognitive assessments, and quality of life scores. Thus, in addition to the surgical procedure, subjects will have 10 direct contacts and 3 telephone contacts with the research team over the 36 week study period (+12 week baseline). This is a standard number of visits for a double-blind placebo controlled study, and equates to approximately monthly visits, with an extra visit at 2-weeks stimulator-on, for up titration of voltage. This time commitment is listed in the PICF.

Many participants will have a degree of intellectual impairment, and consent for them will be provided by a person responsible. These participants will need to be assisted to study appointments, creating a time commitment for the person responsible. This is explicitly stated in the person responsible information and consent form. It is worth noting that carers accompany many of these patients to clinical appointments, and hence participation in the study would extend the time commitment of this pre-existing relationship.

**7.4 Ionising Radiation:**

Radiation: On the day of surgery, a brain CT is performed with a stereotactic frame fixed to the patient’s head, to allow accurate co-registration to pre-operative MRIs. Intra-operatively we perform additional skull x-rays using image intensification x-rays (~8 in total), and short periods of ‘continuous X-ray screening’ to aid electrode placement (~ 10 seconds in total). On the first post-operative day a further CT is performed to precisely determine electrode location, and guide which of the four contacts is optimally located.

**7.5 Definition of Adverse Events:**

Serious adverse events (SAEs) include death, unplanned hospital admission, or status epilepticus. Adverse events (AEs) are any untoward medical occurrence during the trial. For each event the treating doctor will be asked to decide whether or not it was related to device implantation and/or stimulation.

Adverse events will be graded into three categories according to their severity.

Mild – asymptomatic or mild symptoms, clinical or diagnostic observations only. Intervention not indicated. No impact on activities of daily living (ADLs). Self resolving.

Moderate – Minimal, local or non invasive intervention required. Limiting, mild impact on ADLs.

Severe – Severe or medically significant but not immediately life threatening. No requirement for significant invasive intervention (surgery), hospitalisation or prolongation of hospitalisation.

**7.6 Safety Monitoring:**

Safety oversight will be provided by an onsite independent clinician (Professor Sam Berkovic or proxy), aware of group membership (immediate or delayed stimulation). This clinician will be available for stimulator adjustment should there be any stimulation related side effects (eg: precipitation of status epilepticus, or neurocognitive deterioration). Serious Adverse Events will be reported to the HREC within 24 hours of becoming aware of the event. In addition, an independent safety review committee will review the data each six months. This committee is comprised of an independent (off-site) epileptologist and neurosurgeon. The epileptologist is A/Prof Andrew Bleasel who is the Director of Epilepsy and Head of the Department of Neurology at Westmead Hospital and the neurosurgeon is Mr Mark Dexter who is the Head of the Department of Neurosurgery at Westmead Hospital.

**7.7 Battery life:**

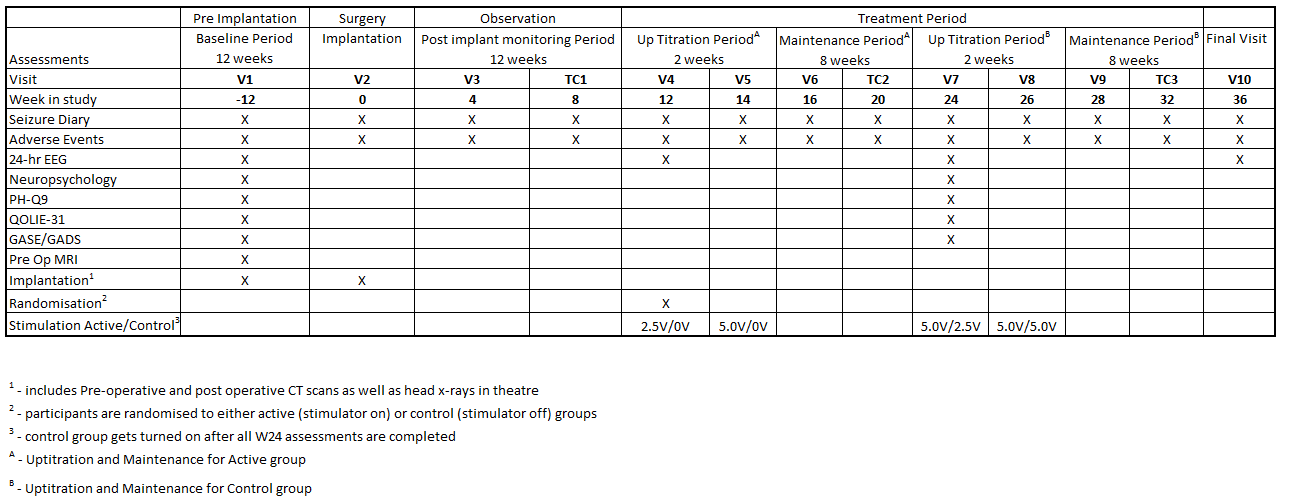
Battery life / replacement: Stimulator battery life is approximately 3-5 years. Around this time, the stimulator becomes no longer able to deliver the programmed voltage, and eventually ceases working. Projected life of the battery can be measured via the ‘programming wand’, which is held over the subcutaneously located stimulator box. When no longer functioning, the stimulator box and wires can be left in situ or removed. If subjects wish to have ongoing stimulation, the old box can be removed and a replacement box connected to the original stimulating electrodes. This is a minor surgical procedure, usually performed as day surgery. At this stage we are not able to offer a guarantee of replacement devices. However, if this study shows benefit, this may form the basis of an application to Medicare for public funding of DBS for LGS.

**8. Budget**

This study has received NHMRC funding, pending ethical approval (project grant number APP1108881, 3 year funding, commencing 2016). Major cost items are the stimulators + electrodes + implantation consumables (30% discounted price from Medtronic), and salaries for a study co-ordinator and part time research assistant (see appendix).

Table 1: Schedule of visits

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  | Pre Implantation | Surgery | Observation | | Treatment Period | | | | | | | |  |  |
|  | Assessments | Baseline Period 12 weeks | Implantation | Post implant monitoring Period 12 weeks | | Up Titration PeriodA 2 weeks | | Maintenance PeriodA 8 weeks | | Up Titration PeriodB  2 weeks | | Maintenance PeriodB 8 weeks | | Final Visit |  |
|  | Visit | **V1** | **V2** | **V3** | **TC1** | **V4** | **V5** | **V6** | **TC2** | **V7** | **V8** | **V9** | **TC3** | **V10** |  |
|  | Week in study | **-12** | **0** | **4** | **8** | **12** | **14** | **16** | **20** | **24** | **26** | **28** | **32** | **36** |  |
|  | Seizure Diary | X | X | X | X | X | X | X | X | X | X | X | X | X |  |
|  | Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X |  |
|  | 24-hr EEG | X |  |  |  | X |  |  |  | X |  |  |  | X |  |
|  | Neuropsychology | X |  |  |  |  |  |  |  | X |  |  |  | X |  |
|  | PH-Q9 | X |  |  |  |  |  |  |  | X |  |  |  | X |  |
|  | QOLIE-31 | X |  |  |  |  |  |  |  | X |  |  |  | X |  |
|  | GASE/GADS | X |  |  |  |  |  |  |  | X |  |  |  | X |  |
|  | Pre Op MRI | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Implantation1 | X | X |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Randomisation2 |  |  |  |  | X |  |  |  |  |  |  |  |  |  |
|  | Stimulation Active/Control3 |  |  |  |  | 1.0V/0V | 2.5V/0V |  |  | 2.5V/1.0V | 2.5V/2.5V |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1 - includes Pre-operative and post operative CT scans as well as head x-rays in theatre | | | | |  |  |  |  |  |  |  |  |  |  |
|  | 2 - participants are randomised to either active (stimulator on) or control (stimulator off) groups | | | | |  |  |  |  |  |  |  |  |  |  |
|  | 3 - control group gets turned on after all W24 assessments are completed | | | |  |  |  |  |  |  |  |  |  |  |  |
|  | A - Uptitration and Maintenance for Active group | |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | B - Uptitration and Maintenance for Control group | | |  |  |  |  |  |  |  |  |  |  |  |  |



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