SRTP - Project Description Form #230

PART I:

Name of Schulich faculty member who will supervise the project	Ana Suller Marti
Supervisor's Schulich, Western, Hospital or Lawson Email	ana.sullermarti@lhsc.on.ca
Schulich Department	Clinical Neurological Sciences

PART II - Project Description

Title of Project	Why Neuromodulation Does Not Work in Some Patients with Epilepsy?

Background

Epilepsy, a prevalent neurological disorder, affects approximately 1% of the population and is characterized by recurrent seizures. Drug-resistant epilepsy (DRE) occurs when a patient fails to become seizure-free after adequate trials with at least two anti-seizure medications. Neuromodulation, involving electrical stimulation through implanted electrodes in the central or peripheral nervous systems, is employed in patients with DRE to achieve functional activation or inhibition of specific neuronal groups, pathways, or networks, for controlling epilepsy. Vagus Nerve Stimulation (VNS) and Deep-Brain Stimulation (DBS) are two available neuromodulation therapies in Canada aimed at reducing seizure frequency and severity. DBS targets various regions, with a predominant focus on bilateral stimulation of the anterior nucleus of the thalamus (ANT-DBS) for multifocal epilepsy and the centromedial nucleus (CM-DBS) for generalized epilepsy. Additionally, the pulvinar is targeted for posterior quadrant epilepsy.

The reduction in seizures across various devices, such as VNS and DBS, is approximately 60%, with a gradual increase over time attributed to the potential 'neuromodulation' effect within the epileptic network. In our center, we have been evaluating potential factors that may influence the response to VNS. Our findings indicate that generalized and focal to bilateral tonic-clonic seizures, as well as generalized epilepsies exhibit more favorable responses.

In contrast, insights into DBS are less comprehensive. Identified factors influencing the response to DBS include precise electrode placement, optimal programing, and careful patient selection. These factors necessitate further investigation to refine treatment approaches, tailoring device adjustments according to the anatomical considerations and specific parameters for each case.

Hypothesis

We have formulated the following hypotheses:

1. Neuromodulation devices have positive outcomes on seizure frequency.

Rationale: Previous studies have shown promising outcomes in reducing seizure frequency with neuromodulation therapies.

2. Neuromodulation devices have a positive impact on overall quality of life.

Rationale: Improved seizure control often correlates with an enhanced quality of life in patients with epilepsy.

3. The efficacy of seizure reduction is influenced by the parameters employed in each neuromodulation device.

Rationale: Differing parameters in device settings may affect the degree of neuromodulation, and consequently,

seizure outcomes.

4. There is a creation of maps because of the volume tissue activation in patients implanted with DBS.

Rationale: Understanding the spatial distribution of tissue activation can provide insights into the mechanisms of action of VNS and DBS.

5. In patients with DBS, the area stimulated will have a direct impact on seizure reduction, while lower tissue activation will have worse outcomes in seizure reduction.

Rationale: Examining the relationship between the location of stimulation and seizure reduction outcomes will help to optimize VNS and DBS interventions.

Proposed Methodology

The proposed study will be a prospective cohort of adult patients with DRE who will undergo VNS or DBS implantation at University Hospital, LHSC, as part of their standard of care for seizure management. The study will involve patient referrals from ten different neurologists within our centre.

Patients will complete easy to administer, brief questionnaires before implantation of the neuromodulation and after implantation (at 6, 12, 24, 36, and 48 months). A literature review and search for validated instruments pertaining to the study's targeted comorbidities identified the following questionnaires:

1) QOLIE-10 to evaluate quality of life

For patients unable to consent themselves, their substitute decision maker will complete the following questionnaires:

1) EQ-5D-5L to evaluate overall health

Questionnaires will take approximately five minutes to complete. Participants will not receive compensation for participation, as all questionnaires will be answered while the patient is at their standard care visits at the clinic. Clinical variables will be obtained from patients' charts (paper and/or electronic), including age at seizure onset, etiological diagnosis, names/number of anti-seizure drugs attempted, seizure risk factors, status epilepticus history, prior electroencephalography findings, neuroimaging abnormalities, results of neuropsychological evaluations, other health conditions, seizure types, mean frequency of seizures, and any history of previous epilepsy surgery, including invasive monitoring. Furthermore, (at 6, 12, 24, 36, and 48 months), we will collect information on the date of neuromodulation device implantation, parameters of the neuromodulation device, seizure outcomes obtained with the device, as well as any associated adverse events., Postoperative outcomes from neuromodulation surgery will be measured using the Engel classification – a classification system used to classify seizure frequency pre- and post-surgery.

Additionally, patients will complete a 3T MRI before device implantation and one-year post-implantation. This MRI will allow better localization of the electrodes and the area activated during seizures.

Expected Outcomes

The objective of this research proposal is to determine the advantages of neuromodulation in patients with epilepsy, specifically in terms of seizure reduction and improvements in quality of life. Furthermore, we aim to personalize the treatments administered, including the targeted stimulation area, to comprehensively understand the impact on seizure frequency. For this analysis we will evaluate the changes in brain connectivity using 3T MRI.

Our project is groundbreaking, addressing the lack of definitive explanations for why certain patients with DRE do not respond to neuromodulation devices. This study pioneers a standardized analysis of all these metrics before and after implantation at different intervals, providing longitudinal insights into the impact of neuromodulation devices on seizures and concurrent brain changes. These findings could revolutionize the treatment of epilepsy patients with mood disorders, offering more effective treatment options. Finally, our proposal has the potential to indirectly reduce the financial burden of epilepsy on the healthcare system. Healthcare costs associated with epileptic patients'

comorbidities are exceptionally high, which reportedly account for 80% of direct medical costs.

Research Environment – Description of the number of research personnel, primary location of research, size of lab, etc

The current research team comprising five experts in neurology and neurosurgery will directly supervise the student, with Dr. Suller Marti as the primary supervisor and Dr. Lau as co-supervisor. The proposed research project will take place at University Hospital, London Health Sciences Centre. Ethics approval for the study has already been obtained.

Names and titles of other individuals who will be involved with the research project?

Dr. Ana Suller Marti, MD, MSc, CSCN-EEG, PhD Candidate, an Epileptologist and Assistant Professor in the Department of Clinical Neurological Sciences at Western University is the Principal Investigator for this research.

Ms. Mariam Elnazali, the Research Assistant supports Dr. Suller Marti in her role. Jayme Arts, as the Research Coordinator, contributes to the smooth coordination of research activities.

Dr. Jonathan Lau, MD, PhD, FRCSC, Assistant Professor of Neurosurgery in the Department of Clinical Neurological Sciences, serves as Co-Investigator.

Can this project be done remotely?	Yes
Duration of Project	Two Summers

Expected Objectives/Accomplishments for Student for Year 1?

In the first year, the medical student involved in our project will assist with tasks such as participant recruitment during clinic appointments, administering questionnaires, collecting and entering clinical data, ensuring participant follow-up questionnaires are completed, and coordinating team meetings.

If the medical student is unable to participate in-person, they could complete all previously mentioned tasks. Follow-up participant questionnaires can be completed via telephone.

Expected Objectives/Accomplishments for Student for Year 2?

In year two, the medical student would assist with the same tasks as in year one. Furthermore, the medical student would have the opportunity to develop and present project abstracts to national and international epilepsy and neurology meetings, including the Canadian League Against Epilepsy (CLAE), the International Epilepsy Congress (IEC), American Epilepsy Society Meeting (AES), and the American Academy of Neurology (AAN). Additionally, the student will actively contribute to manuscript writing for various academic journals, such as Epilepsia, Neurology, Seizure, etc.

PART III - Certifications

If the project will require any certification approvals from one or more of the following offices, please check the appropriate box below.	- Human Ethics
Human Ethics: If you have the protocol information, please enter it below (or enter the status of the approval).	R-20-014

Note: certification approval should be obtained prior to the start of the summer. Projects without this approval will not be a priority for funding.