PROTOCOL

Title: **SURESTEP: Transcranial Direct Current Stimulation in Super Refractory Status Epilepticus (SURESTEP)**

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NCT Number: NCT03819543

Document Date: February 18, 2019

1. Specific Aims

To investigate the efficacy of transcranial direct current stimulation (tDCS) in super refractory status epilepticus (SRSE), defined as:

- Primary Outcome #1: frequency of epileptiform activity on EEG
- Primary Outcome #2: severity of epileptiform activity on EEG (defined along the ictal-interictal continuum)

2. Study Design

i. ICU EEG Monitoring

- The ICU team orders prolonged periods of live EEG monitoring (up to 3 hours at a time) on SRSE patients to determine:
  - whether the patient continues to seize despite the presence of ongoing intravenous anaesthetic
  - whether it is safe to wean anaesthetic
  - whether the patient has stopped seizing off anaesthetic
  - if the patient has resumed seizing off anathesthic, then whether the patient is still seizing once anaesthetic is resumed.
- During business hours, a live ICU EEG monitoring request is automatically honoured by the EEG technologist
- After-hours (from 8 am to midnight for 7 days a week on all 365 days a year), the EEG request is first screened by the on-call neurologist
  - If the request is approved, then the request is forwarded to the EEG technologist.

ii. tDCS Set-Up & Application

- tDCS will only be available when live EEG monitoring is available
  - tDCS can only be applied maximally once a day
    - Only one tDCS session per day
    - tDCS cannot be repeated in one day
  - tDCS can only be applied a maximum of 10 sessions over 10 days
    - Although there is no harm, there is also no perceived benefit if tDCS has not shown benefit after at least 10 sessions of stimulation
- The "HD-targets" software (Soterix Medical, New York) will be used to determine the stimulation parameters to deliver a constant current of 2.0 mA at the epileptogenic foci for 20 minutes
  - HD-targets uses a model human brain to estimate the focal delivery of direct current by adjusting current intensity of 8 channels.
  - If the epileptogenic focus is diffuse or cannot be identified from EEG, then tDCS shall be applied to the right (non-dominant) temporal pole

iii. Real-Time Anaesthetic Management

- Once the EEG technologist has finished their typical clinical set-up, live EEG data will start streaming to a non-blinded EEG reader (an epileptologist or a neurologist with special interest in EEG) at a remote location for interpretation.
- Based on the EEG reader's live report(s) to the ICU team, anaesthetic(s) may be changed
    - If the ICU elects to make no anaesthetic changes, then tDCS shall be applied right away
    - If the ICU elects to increase or decrease anaesthetic, then another 10 minutes shall elapse for the anaesthetic change to take effect prior to tDCS application
- During real-time tDCS application, the EEG reader will determine efficacy by assessing whether there has been enough improvement in the frequency and severity of epileptiform activity (primary study outcomes #1 and #2) to warrant discontinuation (or continued discontinuation) of intravenous anaesthetic sedation to the end of the EEG recording (secondary study outcome)
    - Frequency of epileptiform activity (primary outcome #1) is defined as the number of discharges per unit time (e.g. spikes per minute)
    - Severity of epileptiform activity (primary outcome #2) is defined by the morphology of the activity as outlined by the American Clinical Neurophysiology Society Standardized Critical Care EEG Terminology for the interictal-ictal continuum (e.g. spikes or sharp waves are more epileptiform than broad sharp waves or sharply contoured activity)
    - If tDCS unexpectedly worsens epileptiform activity, tDCS will be terminated immediately
- After tDCS application is complete, the RA will remove all tDCS equipment from the patient and the bedside
- The EEG reader will continue live-monitoring the study to ensure that any changes in the frequency and/or severity of epileptiform activity are enduring (i.e. persist through to the end of EEG recording)
- Total EEG recording will be 3 hours as per the usual maximum ICU EEG recording duration protocol

3. Statistical Analysis Plan

- The primary study outcomes of epileptiform activity frequency before, during, and after tDCS will be analyzed on a per-stimulation session basis
- The primary study outcomes of epileptiform activity frequency before, during, and after tDCS will also be analyzed on a per-patient session basis by averaging spike rates for all sessions in that patient
- All data will be assessed for normality using the Shapiro-Wilk test

- Parametric tests will be used for normally distributed data and non-parametric tests will be used for non-normally distributed data in order to test before vs. during tDCS on per-session and per-patient bases; and before vs. after tDCS on per-session and per-patient bases