Effect of Antiseizure Medication in Seizure Networks at Early Stages of Acute Brain Injury. The Rs-fMRI, Open-label Pilot Trial.

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Master Protocol Document

Title	**Effect of Antiseizure Medication in Seizure Networks at Early Stages of Acute Brain Injury. The Rs-fMRI, Open-label Pilot Trial.**
Sub-Title	Seizure network treatment in Coma
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Research Sites	Neuroscience Intensive Care Unit Pediatric Intensive Care Unit
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IRB approval and study ID number: 23-0157

I have read, understood, and approved this version of the protocol.

Principal Investigator: Varina Louis Boerwinkle Date: October 28, 2024

Principal Investigator: Emilio Garzon Cediel Date: October 28, 2024

Statistical Co-investigator: Hongtu Zhu Date: October 28, 2024

Table of Version Changes

Previous Version No.	Affected Sections	Summary of the Changes to the Protocol	Reason for Changes
1	**1**	The whole protocol synopsis was rearranged, also modifications regarding aims, the age and intervention were done.	it was completed and modifications were done to address imprecisions
1	**3.1**	We stated that developing prediction models epileptogenicity in early SABI was the intention of a different future trial.	To clarify that developing prediction models epileptogenicity in early SABI is outside of the scope of this trial
1	**3.2**	We clarified that the proportions estimation will be done on the initial rs-fMRI.	To make clear the temporal relationship with the intervention
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1	**WHOLE DOCUMENT**	Age range was corrected to be unified 6-65 years.	To make clear the temporal relationship with the intervention
1	**3.5**	The information inclusion time was restricted to specific 14 months after enrollment started.	To guarantee the study duration, because the participants' duration for this Aim cannot be predicted with certainty.
1	**4.1**	We specified that the clinical team can modify the “maintenance” dose before the 2nd rs-fMRI is obtained.	For better understanding.
1	**4.1**	WE clearly stated that our intervention is off-label but it meets the requirements to do not require submission of an IND to the FDA.	To address the concern about use of off-label interventions.
1	**4.1**	We listed al five possible medication combos and dose adjustment rules	To make clear the potential regimens.
1	**4.3**	We added comments regarding extended age range.	To address the concern about the wide age range.

1	**4.3**	We added details regarding the EEG recordings.	To address the concern about reproducibility.
1	**5.2**	Contraindications for MRI scan.	The main study variables are based on MRI data.
E	**5.2**	Inclusion criteria modified: The potential days from acute brain injury to enrollment where change from 1-45 to 3 (72 Hours)-45.	The first 72 Hours are critical in the stabilization of the patients, so this improves the homogeneity of the subjects.
1	**5.2**	exclusion criteria modified: "Speaking fluently or at their prior reported baseline mental status by medical chart review before the intervention starts."	For better reproducibility
1	**5.2**	Selection criteria specified: "If there is medical history of neurological conditions with concerning for impaired independence and the functional status of the patient cannot be properly addressed, the patient will be excluded from participation."	For better reproducibility
1	**5.3**	I was detailed that Barthel Index Score is asked after verbal informed consent for screening.	For clarity about the informed consent for screening.
1	**5.3**	We added "EEG in this protocol does mean continuous video EEG, which is the stand of care for UNCH ICU patients".	For clarity about the routine EEG
1	**5.5**	The screening -enrollment process was further explained.	For clarity about the sampling
1	**6**	Bullet point for the intervention activities.	To clarify time frames for the activities.

1	**7.2. & 7.3**	Screening and enrollment were reworded and activities list with timeframes where added.	To clarify time frames for the activities.
1	**7.5**	References to the PASS clinic tests were added. It was clearly state that PASS clinic follow-up is UNC hospitals SOC, so the information from this clinic will be just collected from medical charts.	To clarify the present study is not responsible for the schedule or tasks related to the PASS clinic.
1	**7.8**	The dropouts are explained with more detail.	To clarify the dropouts.
1	**8.3**	Included an intercept to represent the mean difference before and after ASM in the model and use the t-test statistic to test. whether the intercept is equal to zero for Aims 1a and 1b.	to improve the interpretation of aim 1.
1	**8.3**	For Aims 3 and 4 the statistical analysis method was changed from linear regression to logistic regression.	the variables EEG improvement and RSN improvement are binary variables.
1	**4, 5.2, 5.3, 7.2, 7.3**	The word liaison was replaced for Legal authorized representative.	To match the frequent language.
1	**11**	Blood sample collection and processing was included.	For dose adjustment of phenobarbital.
1	**12.2, 12.3, 12.4**	The independent safety monitor will classify the AE and decide which AE require a safety meeting to review its classification and generate the report.	To optimize the report of the AEs.
1	**12.2, 12.4, 12.5**	SAE will pause the trial. The resuming conditions were further clarified.	To make clear situations of study pause and study end.

1	**13.1.2**	Dispositions for reconsenting subjects that may regain decision-making capacity were added.	Some Subjects may regain decision-making capacity.
1	**13.5**	The ISM was changed.	To make it different from the PI.
2.1	**4**	We Properly defined SzNET-	For clarity in the diagrams
2.1	**1, 3, 8.3**	The aim 5 whas modified from collect to describe	To describe better what we are going to do with the data
2.1	**4**	We added feasibility and confounder variables	To leverage the study to support similar future trials' methods.
2.1	**1, 3, 4, 8**	We included an additional aim for feasibility	To leverage the study to support similar future trials' methods.
2.1	**11.3**	It was specified the purpose of the Phenobarbital serum levels and their record keeping	For clarity
3	**4.3**	Aim 5 variables where changed to Exploratory	This is more exploratory than secondary aim.
3	**4.1**	All dose regimens where specified for pediatric and adult population	For more precise reference

3	**12.3**	It was specified that the anatomical MRI sequences will be reported by the Radiology department.	To make the distinction from the functional MRI sequences reviewed by the research team
3	**5.2**	Exclussion criteria added: Treating physician determines the patient is no candidate to receive 2 of the 5 protocol-specified ASM.	Specified because of IRB request.
3	**5.2**	Replaced "Speaking fluently or at their prior reported baseline mental status by medical chart review before the intervention starts" by "Following Commands in 3 different exams from at least 2 different providers."	To have a more unequivocal criteria
3	**4.3**	More explicit etiologies were included among the allowed variables.	To match the CRF design which is more descriptive, allowing to check multiple etiologies by each case.
3	**1,3,4,5,6,7,8,10**	PASS clinic was replaced by "one of the NSICU Post-Dischrage clinics."	To also include the follow-up fro patients scheduled to any one of the NSICU Post-Dischrage clinics.
3	**1, 5, 13**	The Medical ICU from UNC health was included as a place of enrollment	Most of the hypoxic hisquemic SABI patients are treated in this ICU
3	**4.3**	The features to be evaluated by the EEG improvement variable were further specified	To have a more standardized definition of EEG improvement
3	**6**	A restriction was added to prevent patients with vasospasm detected by transcranial Doppler from undergoing the rs-fMRI scan.	To avoid scanning the participant under radiological vasospasm and enhance findings reproducibility.
4	**1, 2, 3, 4, 5, 7, 8, 12**	Increase the GCS threshold to GCS<13 in the inclusion criteria.	To allow the participation of patients with moderate acute brain injury too.

4	**1, 2, 5, 7**	Inclussion criteria were reworded to state that the GCS as inclusion criteria will be verified at enrollment instead of at admission.	To allow the participation of patients whose consciousness suppression started after ICU admission.
4	**1, 2, 3, 4, 5, 7, 8, 12**	Modified the aims to study population with moderate to severe acute brain injury (MABI) instead of just severe aute brain injury (SABI)	To increase the enrollment rate.
4	**1, 4, 6, 12**	The intervention regimen options were reduced for the subgroup of participants with GCS 9 to 12, not allowing phenobarbital as one of the intervention ASM and indicating that the Loading dose of one of the ASM will be omitted.	To keep a favorable risk-benefit relationship for the participation of that subgroup of patients.
4	**1, 5, 7**	The allowed time from injury to enrollment was increased from 3-45 days to 2-90 days.	To increase the enrollment rate.
4	**4, 6**	A repeated loading dose of phenobarbital is indicated in the phenobarbital dosing adjustment after the phenobarbital levels.	To align with the NSICU current clinical practice and obtain therapeutic drug lvels faster.
4	**1, 5, 13**	three ICUs fron UNC hospitals, were included as enrollment sites and will be screened for potential participants.	To increase the recruitment rate.
4	**6**	The timming to upload the rs-fMRI #1 and #2 reports to EPIC was specified.	For clarity on the procedures.
5	**4.1, 6**	Oral/enteral maintenance doses regimens were included for levetiracetam and lacosamide	The pharmacodynamics are comparable and allowing this routes the protocol is more aligned with the standard of care
6	**1, 4, 5**	The inclusion criteria extended the enrollment age from 18 months up to 70 years.	To increase the enrollment rate.

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Statement of Compliance

This study will be conducted as specified in the protocol and in accordance with the *International Conference on Harmonisation Guidelines for Good Clinical Practice* (ICH E6) and the *Code of Federal Regulations on the Protection of Human Subjects* (45 CFR Part 46).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the *Institutional Review Board* (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

If required by the IRB, the master protocol document, informed consent form(s), recruitment materials, and all participant materials will be submitted to the *Scientific Review Committee* (SRC) prior to IRB review (research.unc.edu/clinical-trials/src).

The statistical analysis plans will be consistent with guidance in CONSORT Statement [1] or STROBE Statement [2], ICMJE recommendations [3], the 2016 and 2019 statements of the American Statistical Association [4,5], and recommendations in Nature [6,7].*

All personnel involved in the conduct of this study have completed human subjects protection training.

Table of Abbreviations

AE	Adverse events
ASM	Antiseizure medication
BIS	Barthel index score
BOLD	Blood oxygen level dependent
CRF	Case Report Form
CI	Confidence interval
CICU	Cardiac intensive care unit
CT	Clinical Trial
CTICU	Cardiothoracic surgical intensive care unit
CTCAE	Common terminology criteria for adverse events
DoC	Disorders of consciousness
EEG	Electroencephalogram
EEG -	Patients without electrographic seizure, electroclinical seizure or ictal-interictal continuum
EEG+	Patients with electrographic seizure, electroclinical seizure or ictal-interictal continuum
GCP	Good clinical practice
IC	Independent component
ICA	Independent component analysis
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICF	Informed consent form
ICU	Intensive Care Unit
IND	Investigational New drug Application
ISM	Independent Safety Monitor
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
IRB	Institutional Review Board
LAEP	Liverpool Adverse Event Profile Test
LAR	legally authorized representative
MD	Maintenance dose
MICU	Medical Intensive Care Unit
MPD	Master protocol document
MRI	Magnetic resonance imaging
MSABI	Moderate to severe acute brain injury
N	Number of enrolled participants
NC TracS	North Carolina Translational and Clinical Sciences

* [1] www.consort-statement.org
[2] www.strobe-statement.org
[3] www.icmje.org
[4] Wasserstein RL, et al. (2016), The ASA's Statement on p-Values, ***The American Statistician***, 70:2, 129-133
[5] Wasserstein RL, et al. (2019), Moving to a World Beyond p < 0.05, ***The American Statistician***, 73:sup1, 1-19
[6] Amrhein, et al. (2019) Scientists rise up against statistical significance, ***Nature*** 567, 305-307
[7] Editorial (2019) It's time to talk about ditching statistical significance: Looking beyond a much used and abused measure would make science harder, but better. ***Nature*** 567, 283-283.

NSICU	Neuroscience intensive care unit
NHI	National Institutes of Health
NINDS	National Institutes of Neurological Disorders and Stroke
NNDI-E	Neurological Disorders Depression Inventory for Epilepsy
PI	Principal investigator
PICU	Pediatric intensive care unit
PROMIS	Patient Reported Outcome Measurement Information System
PS	Power spectrum
PSI	Power spectrum improvement ratio
OHRP	Office for Human Research Protections
QC	Quality Control
QOLIE	Quality Of Life In Epilepsy
RCT	Randomized controlled trial
RS	Resting state
Rs-fMRI	Resting state functional MRI
RSN	Resting state networks
SABI	Severe acute brain injury
SICU	Surgical intensive care unit
SOC	Standard of care
SOM	School of Medicine
SOP	Standard operating Procedures
SzNET	Seizure networks defined by resting state functional MRI
SzNET-	That has presence of Seizure networks observed in resting state functional MRI #1
SzNET+	That has presence of Seizure networks observed in resting state functional MRI #1
TE	Echo time
T-MoCA	Telefonic Montreal Cognitive Assessment
TR	Repetition time
TraCS	N.C. Translational and Clinical Sciences Institute (tracs.unc.edu)
TV	Total volume
TVR	Total volume reduction
UNC	The University of North Carolina
UNCH	UNC Hospitals
UP	Unanticipated Problem

1. Protocol Synopsis

Title	**Re**sting state fMRI **B**OLD **O**ffers **O**pportunity for **T**reatment in **C**oma
Study Description	This is an open-label pilot clinical trial in the PICU, NSICU, SICU, CTICU, CICU, and MICU at UNCH to characterize the behavior of Seizure Networks (SzNET) in 18 months to 70 years old patients with moderate to severe acute brain injury (MSABI) and suppression of consciousness. It will assess the reduction of SzNET after antiseizure medication (ASM) using pre/post-treatment rs-fMRI and compare that response to EEG and normal resting state networks (RSN).
Specific Aims **(objectives)**	**Aim 1.** Estimate the degree of improvement of SzNET in MSABI patients after intervention. **Aim 1a**. Measure the improvement of the SzNET total volume in MSABI patients after the intervention. **Aim 1b**. Measure the improvement of the SzNET power spectrum in MSABI patients after the intervention.

	Aim 2. Estimate the proportion of EEG- and EEG+ patients presenting SzNET on the initial rs-fMRI. **Aim 3.** Investigate association between pre/post-intervention EEG improvement and SzNET response. **Aim 4.** Investigate the association between the intervention responses of the normal resting state network connectivity and the SzNET in MSABI patients. **Aim 5.** Describe psychosocial functional measure outcomes and ambulatory ASM toxicity at 3 months from discharge. **Aim 6.** Assess the trial's design success regarding participants enrollment and retention. **Aim 6a**. Measure the enrollment rate. **Aim 6b**. Measure the dropout rate.
Target Population	**Inclusion Criteria** 1. Age from 18 months to 70 years. 2. Suppression of consciousness related to a neurological injury. . 3. GCS less than 13. 4. Acute brain Injury by TBI, hypoxic-ischemic Insult, cardiac arrest, or Stroke. 5. 2 to 90 days from MSABI to enrollment. 6. Have a routine clinical care surface EEG performed after the admission to PICU, NSICU, SICU, CTICU, CICU or MICU. 7. Hospitalized at PICU, NSICU, SICU, CTICU, CICU or MICU **Exclusion Criteria** 1. Previous medical history of Epilepsy. 2. Previous medical history of neurological conditions that lead to dependence greater than expected for age on care for basic daily activities given by Barthel Index score (BIS) less than 80. 3. Brain death. 4. Currently able to speak fluently. 5. Currently at one's prior reported baseline mental status. 6. Known allergy/Hypersensitivity or medical contraindications (like porphyria or cardiac arrhythmias) to the treatment protocol options, leaving no potential combination of drugs for the intervention without concerns for adverse events related to known preexistent conditions.. 7. Prisoner human subjects by medical chart review. 8. Pregnant. 9. Treating physician determines the patient is no candidate to receive 2 of the 5 protocol-specified ASM.

	10. Contraindications for MRI scan.
Numbers of Enrollees	Up to 68 individuals will be screened with the goal of enrolling 54 eligible individuals and identifying a subset of 22 participants who are SzNET positive (see Study Schema, Figure 2). Using a quota sampling strategy, 11 SzNET+ patients will be recruited consecutively for each EEG+ and EEG- strata to ensure the necessary number of patients for the interventional phase of the study.
Interventions	Participants that are SzNET positive will receive a loading ASM combination dose of Levetiracetam (60mg/kg) and Phenobarbital (20 mg/kg), followed by maintenance dosing for weight and age of both medications from three to ten days until the repeat rs-fMRI. If care team considers either of those medications cannot be used, then they are allowed to administer any other combination of two ASM from the following list as the loading dose: 1. Phenobarbital 20 mg/kg 2. Levetiracetam 60mg/kg 3. Lacosamide 10 mg/kg 4. Valproate 30 mg/kg 5. Fosphenytoin 20 mg/kg Maintenance dose: Standard dosing for weight and age of both medications used for the loading dose from three to ten days until the repeat rs-fMRI. Participants with GCS 9 to 12 will not be assigned phenobarbital as one of the intervention ASM and the loading dose of one of the two ASM selected will be omitted. In this case the ASM list doses remain the same, and the recommended intervention will be Levetiracetam with loading and maintenance doses and lacosamide only maintenance doses. For all participants, the protocol driven ASM can be continued, suspended of modified by the care team after the repeat rs-fMRI is obtained. ASM administration after the follow up scan is not considered part of the protocol intervention. Step-wise withdrawal is encourage in case the care team decides to suspend the ASM given as part of the protocol.
Outcome Measures	Definitions are provided in the abbreviations table. **Aim 1.** Pre and Post treatment SzNET activity **Aim 1a.** Pre and post-treatment SzNET total volume medians **Aim 1b**. Pre and post-treatment SzNET power spectrum medians **Aim 2.** Presence of SzNET in rs-fMRI #1 (binary) **Aim 3.** Follow-up EEG improvement (binary).

	Aim 4. Connectivity improvement of typical RSN in MSABI patients after intervention (Binary). **Aim 5.** Follow up outcomes (3 months from hospital discharge) collected from one of the NSICU Post-Discharge Clinics, include: NDDI-E, PROMIS emot. Dist. -Anxiety - Short form, Liverpool Adverse Events Profile questionnaire, QOLIE-10-P and MoCA **Aim 6.** **Aim 6a.** Enrollment rate. **Aim 6b.** Dropout rate.
Statistical Analysis Plans for Each Aim	**Aim 1 Plans.** Use linear regression to test Aim 1 **Aim 2 Plans.** Calculate the proportions and use the two-proportion Z-test to test their difference. **Aim 3 Plans.** Use logistic regression for Aim 3. **Aim 4 Plans.** Use logistic regression for Aim 4. **Aim 5 Plans.** Calculate the summary statistics for Aim 5. **Aim 6 Plans.** Calculate enrollment and dropout rates
Study Duration	16 Months
Participation Duration	For main aims 5 to 14 days. Allowed patients for the exploratory aim number 5 will have a variable participation duration because of an unpredictable hospital discharge time.
Enrollment Duration	1 year

2. Introduction

2.1. Background Information

Disorders of consciousness (DoC) are common in severe acute brain injury (SABI). SABI with prolonged DoC has high mortality, morbidity, and long recovery with high costs [1-3]. A treatable contributor to DoC in SABI is seizures, with 30-50% incidence by EEG, and 34% of these are subclinical[4-7].

However, surface EEG monitoring techniques have lower sensitivity for detecting seizures in deep brain locations. A significant knowledge gap is what should be done for the patient when the EEG is not conclusive for seizures activity (EEG-), and yet the patient's consciousness is not improving. Because moderate to severe brain injury (MSABI) causes injury to deep locations of the brain, there could still be seizures coming from these locations but they may not propagate epileptiform activity to the brain's outer millimeters where the scalp electrodes can sense it[8]. Thus, it is unknown, "***To what extent does EEG insensitivity in MSABI causes underestimation of epileptogenic activity?***". Thus, in this situation, a more sensitive technology of epileptogenic network activity in deeply located brain regions is needed.

Unfortunately, a current non-invasive and safe means of determining if seizures are reducing consciousness in MSABI is not established. The impact of this clinical gap has resulted in the lack of professional societies' guidelines with evidence-based recommendations for antiseizure medication (ASM) in those with SABI and EEG-[9,10]. This knowledge gap and its consequences has long been recognized by physicians, resulting in widely accepted use of empirical ASM, hoping for the patient to improve when other reasons for coma have been ruled-out.

One noninvasive and safe solution to address this problem is seizure networks (SzNET) detection by resting-state functional MRI (rs-fMRI). Rs-fMRI is sensitive to seizure network activity in deep locations primarily during interictal periods[11-13]. SzNET are pathological in those with known seizures, which is supported by the improvement of epilepsy surgery outcomes when SzNET are targeted[14], and SzNET normalization correspondingly with the post-operative seizure reduction[13].

However, what this abnormal connectivity in MSABI is caused by is not established. Multiple contributors to the abnormal connectivity in MSABI are possible. In addition to seizures, others include increased intracranial pressure from edema, hemorrhage, or hydrocephalus, or alternatively, cortical spreading depolarizations [15,16]. ***If the abnormal network patterns in MSABI correspond to those seen in seizure networks of epilepsy and are modulated by antiseizure medication, then there may be a relationship with epileptogenic brain activity.*** While this is not definitive proof of epileptogenic causation or change in outcome, instead ASM delivery in those with MSABI and seizure networks is an initial logical perturbation of this complex network system to determine if further investigation is warranted.

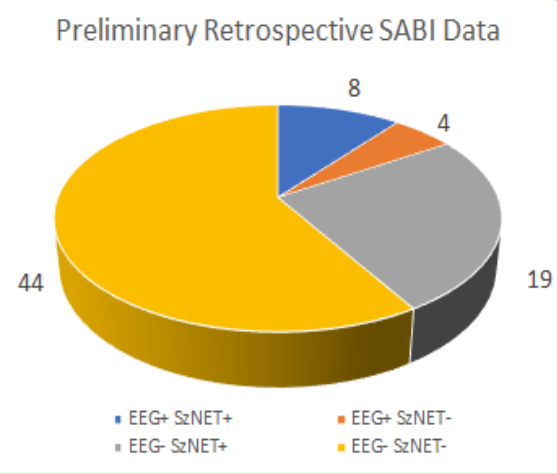


Figure. 1. Adult and Peds SABI EEG and Seizure Network (SN) prevalence (N=63). EEG-SN+ comprise 30% of the SABI population.

Table 2. Treated SzNET

Treatment: 5 of 6 patients with phenobarbital load 20 mg/kg x 3 days and 1 patient with levetiracetam load 60 mg/kg	
EEG-	60%
DoC improvement*	100%
SzNet improvement	100%
EEG improvement in those EEG+	100%

*DoC improvement defined by care teams' documentation of patient exam improving by one level of DoC within 14 days of therapy. Example from coma to unresponsive wakefulness syndrome (UWS), or from UWS to minimal responsiveness syndrome (MCS).

In our preliminary retrospective SABI data in adults and children (N=63), 30% were EEG- and *SzNET*+ (**Fig. 1**). Regarding initial evidence of *SzNET* response to ASM in SABI, of the 63 SABI patients who received rs-fMRI, 27 (42%) had SzNet; of these, 6 received ASM therapy driven by clinician interpretation of rs-fMRI results described in Table 2 with network and outcome improvement.

In epilepsy, *SzNET* also disrupt the RSN, impacting the patient phenotype, such as memory capacity reduction[17,18]. Since Resting State Networks (RSN) connectivity is associated with consciousness recovery in DoC[19,20], then ***SzNET may also be disrupting RSN connectivity in MSABI, producing prolonged DoC***. In our case series SABI- *SzNET* treatment experience described in Table 1, the RSN connectivity also improved with therapy. Thus, it is also possible that by tracking not only the therapy impact on *SzNET* but also the RSNs, especially the default mode network, that is highly associated with SABI DoC recovery[21,22], we may better understand the link of *SzNET* disruption of RSN and possible mechanism of prolonged DoC in SABI.

Our long-term goal for this research line, aimed to be through the support of the NINDS, is to evaluate *if and how SzNET and RSNs are linked to epileptogenic activity and connectivity in consciousness-supporting networks in SABI, thereby elucidating the opportunity for DoC SzNET-guided therapy, and potential for improved outcomes of this subset of DoC.* Supportively, the goal of this initial proposal is to allow for the opportunity to acquire adequate pilot data to inform the

larger planned and more rigorous trial, which will be a double-blinded placebo controlled clinical trial of ASM in SABI patients who are EEG- and SzNet+.

Thus, we hypothesize that SzNET may hinder the improvement of coma, by reducing typical resting state network connectivity.

2.2. Scientific Rationale

Study Proposal: This is an uncontrolled two-arm open-label single-center interventional clinical trial that will be used to prepare for a full-scale randomized, placebo-controlled trial by investigating the feasibility of the study and proposed measures collection. It will explore changes in SzNET, RSNs, and EEG data, before, and after combination drug therapy with levetiracetam and phenobarbital (or a combination of two other ASM drugs (see section 4.1) and psychometric measures at 3 months after hospital discharge based on a sample of 54 patients with MSABI and DoC. Our long-term goal for this research line is to determine if SzNET are linked to epileptogenic activity in SABI to improve the endotype characterization of its DoC and better guide targeted treatments.

Rational for specific aims and outcome measures: The purpose of this study is to determine the occurrence of a specific biomarker called SzNET in patients with MSABI and investigate the effects of ASM on SzNET. The study also aims to find any correlation between EEG and SzNET in patients who experience seizures on EEG.

The study outcome measures will focus on quantifiable changes in SzNET and RSNs with therapy. It is difficult to isolate the effects of early therapy on outcomes due to the high rate of withdrawal of life sustaining therapy in the early weeks of MSABI and the potential secondary injuries. Therefore, this study will take a conservative approach and focus on quantifiable changes in SzNET and RSNs with therapy. If there are no significant changes in the networks after therapy, it may not be necessary to further investigate the relationship between SzNET and outcomes. The feasibility of collecting outcomes and trends in relation to SzNET will be tested as part of this pilot study through ICU exams and follow-up clinics, including side effects of medication, morbidity, and mortality, to identify any positive trends.

Rational for study inclusion/exclusion criteria: This study focuses on patients with brain damage severe enough to impair consciousness but with the potential to recover in the absence of epileptogenic activity. The inclusion criteria have been chosen to identify patients with this level of brain damage.

To be eligible for the study, patients must have a suppression of consciousness related to a neurological injury with Glasgow Coma Scale of less than 13 and be hospitalized at the ICU. This brain injury severity score indicates that the patient has a moderate to severe consciousness compromise, which is the intended target population. Patients who have recovered their baseline mental status or the ability to follow commands prior to therapy are excluded from the study or withdrawn if they were already consented into the study. This exclusion ensures that eligible participants still has a disorder of consciousness severe enough to warrant the risk of the study therapy. Patients who are brain dead are also excluded from the study because their lesions are so severe that recovery is not possible, regardless of the treatment.

Rational for study intervention:
The relationship between SzNET, EEG, and epileptogenic activity in patients with MSABI is not yet fully understood. To validate SzNET, it is necessary to explore its meaning in patients who are EEG-negative, as they are the population that could potentially benefit from it the most, given the possibility of epileptogenic activity overlooked by EEG. Validating seizure-biomarkers in surface EEG-negative patients is challenging, as the alternative gold standard validation methods should be the intracranial EEG which would propose higher risk in the target population for increased bleeding and infection risks. By administering an ASM and observing the induced changes in SzNET and RSN we may document a response like the observed in the patients referenced in table 2. If we can gather

preliminary information consistent with our pilot findings, that may justify conducting a larger randomized controlled trial (RCT).

Rational for two ASMS and dosage:
When the EEG is positive, we can track a patient's response to medication, but we won't have a similar bedside measure of immediate improvement in patients who are EEG-negative but have positive SzNET. If SzNET is contributing to a patient's depressed mental status as occurs during non convulsive status epilepticus, Its severity could be similar.

Since we cannot measure improvement by EEG, and because more than one medication is often required in status epilepticus, we need a strategy with a high likelihood of controlling epileptogenic activity. Dual loading doses of ASM have been shown to provide a more definitive response in known cases of status epilepticus than using only one medication[23,24]. The selection of phenobarbital is due to its relatively high efficacy in status epilepticus[25,26]. The primary concerning side effect of phenobarbital is ventilatory depression. However, this effect is less relevant in this population as many of these patients already have a secure airway due to the ongoing depression in mental status and required mechanical ventilation. Therefore, this is not a significant concern for patients who are already under mechanical ventilation due to their low neurological response.

3. Specific Aims

3.1. Aim 1

Obtain a preliminary estimate of the seizure networks (SzNET) changes in moderate to severe acute brain injury (MSABI) patients after the research intervention with antiseizure medication (ASM) to support a future larger placebo controlled resting state-fMRI (rs-fMRI) clinical trial for prediction models of epileptogenicity in early SABI. The preliminary data of primary interest is the magnitude of the functional imaging SzNET response to high-efficacy pharmacological treatments in this clinical setting.

Aim 1a

Measure the improvement of the SzNET spatial total volume (TV) in MSABI patients after the intervention. The estimand of interest is the SzNET spatial TV median before and after the intervention in the target population. The intrasubject TV change ratio will be expressed as total volume reduction (TVR).

Aim 1b

Measure the improvement of the SzNET temporal power spectrum (PS) in MSABI patients after the intervention. The estimand of interest is the SzNET temporal PS median before and after the intervention in the target population. The intrasubject PS change ratio will be expressed as power spectrum improvement (PSI)

3.2. Aim 2

Estimate the frequency of EEG- and EEG+ patients presenting with SzNET on their initial rs-fMRI prior to the study intervention. The estimands of interest are the proportions and differences of proportions of patients with SzNET among EEG- and EEG+ patients in this clinical setting.

3.3. Aim 3

Investigate association between post-intervention EEG improvement and SzNET response. The estimand of interest is the relative risk of EEG improvement in patients with more than 50% improvement of their SzNET by TVR and PSI.

3.4. Aim 4

Investigate the association between the post-intervention typical resting state networks (RSN) connectivity improvement and the SzNET response. The estimand of interest is the relative risk of improvement of the RSNs in the patients with more than 50% of improvement of their SzNET by TVR and PSI.

3.5. Aim 5

Describe psychosocial functional measure outcomes and ambulatory ASM toxicity at 3 months from hospital discharge. The estimates of interest will be the PROMIS Emotional Distress—Anxiety— Short Form, the Neurological Disorders Depression Inventory for Epilepsy (NNDI-E), the QOLIE-10-P, the Telephonic Montreal Cognitive Assessment, and the Liverpool adverse event profile test. All will be assessed at the 3 month follow up visit by one of the NSICU Post-Dischrage clinics. This aim only applies to the patients that are discharged alive from the hospital and will include results from visits until 14 months after the enrollment start.

3.6.Aim 6

Assess the trial's design feasibility success in enrollment and retention for our actual institutional context by evaluating the enrollment rate and dropout rate among participants at the end of the trial. it will be composed by two sub aims.

Aim 6a

Measure the participants enrollment rate during the hole study enrolling months. The estimand of interest will be the rate of enrolled patients per month.

Aim 6b

Measure the participants dropout rate among participants. The estimand of interest will the dropout rate from the total enrolled participants at the end of the study.

4. Study Design

This is a prospective interventional, uncontrolled, open-label, single center pilot study in moderate to severe acute brain injury (MSABI) patients with suppression of consciousness. The study main outcomes require pre and post-intervention rs-fMRI data collection to characterize the evolution of SzNET, a physiological measure of brain function. Clinical implementation of rs-fMRI is still novel, not frequently performed at early stages of MSABI, and has few medical indications as a follow-up test. As this data is infrequently generated during the standard of care (SOC), a prospective interventional study with an ASM intervention and a research funded rs-fMRIs is needed.

The target population is in the UNC intensive care unit, and to prioritize the human subjects' wellbeing, the patients will receive their standard clinical monitoring and therapy per the local care team, including EEG, antiseizure therapy, and head imaging as clinically indicated. Once stable for MRI, subjects will receive the study-related rs-fMRI #1. If SzNET are detected (SzNET+), the subject will start the study treatment protocol, followed by post-treatment repeat rs-fMRI (rs-fMRI#2) and EEG. Those patients negative for SzNET in the rs-fMRI#1 (SzNET-) will not

have intervention or research follow up EEG and rs-fMRI, but if they are followed by one of the NSICU Post-Dischrage clinics, the information obtained from their assessments will be collected as part of this study.

Rationale for intervention with ASM

The purpose of this study is to test the correlation of SzNET in MSABI with epileptogenic activity. To benchmark this correlation, we will compare the response of SzNET to ASM with well-known effect in the epileptogenic activity. Previous data in epilepsy shows that SzNET improvement is related to clinical improvement[13], and those clinical effect sizes of seizure improvement have been measured for multiple pharmacological treatments including the ones listed for this protocol intervention[26,27]. We hypothesize that SzNET improvement will be similar to the effect size expected for the selected ASM. If we are correct, SzNET could help predict clinical outcomes related to epileptogenic activity. To achieve this, we need treatment protocols with proven consistent clinical response and a large effect size. The recommended protocol for a effective response is a combination of intravenous phenobarbital and levetiracetam at loading doses[26]. However, since the main outcome measures are quantitative and smaller effect size responses could still be detected, for this pilot trial we allow a list of alternative ASM protocols with anticipated similar efficacy. The purpose of this alternative options is that the care team can use a different protocol if it is more appropriate given the patient's particular characteristics.

Rationale for stratification by EEG

Restated: Seizure network activity could be the cause of suppressed conscious in acute brain injury. The EEG, which is the best current test for detection of seizure, may not detect this activity, if it is occurring in deep brain locations. SzNET by rs-fMRI may be a biomarker of abnormal activity in acute brain injury that could be responsive to ASM.

In ICU patients with suppression of consciousness, we will use the EEG to stratify patients into two groups, EEG+ and EEG-. EEG+ will be defined by either electrographic seizure, electroclinical seizure or ictal-interictal continuum as defined by the American clinical Neurophysiology Society's Standardized Critical Care EEG Terminology[28], whereas EEG- will be lacking these features. Further, we will observe the rate of SzNET by rs-fMRI in both groups, and response of the SzNET and EEG to study intervention.

To ensure rapid recruitment, the study will use a quota sampling strategy. Specifically, eleven SzNET+ patients will be recruited consecutively for each EEG+ and EEG- strata to ensure the necessary number of patients for the interventional phase of the study.

Data collection

First, informed consent will be obtained from the subject's legally authorized representative (LAR). Then, baseline variables will be collected by interview and review of medical charts. After subjects are scanned, the rs-fMRI images are uploaded to the UNCH MRI PACS system by an MRI technician and accessed through the UNCH secure PACS portal by study personnel, through download onto the UNC SOM secure system. There, the rs-fMRI processing and analysis are accomplished, and information is deidentified for storage in the PI's UNC-OneDrive. Clinical and demographic data will be collected by the study research coordinator and stored in a REDCap file. Once the study data collection is completed, the deidentified REDCap database will be used for analysis and stored at the PI's UNC-OneDrive. A separately stored subject key code in a SOM-stored research excel file will link the research subject's codes and MRN until five years after study completion. Hospital discharged patients will be followed through one of the NSICU Post-Dischrage clinics, and that data will be stored in the same study REDCap file.

End-of-study criteria and discontinuation criteria for the participant.

Patients that need to discontinue the study treatments during the intervention phase because of medical reasons will be withdrawn from the study, unless they can be assigned to one of the alternative combination-drug protocols and continue to meet eligibility criteria.

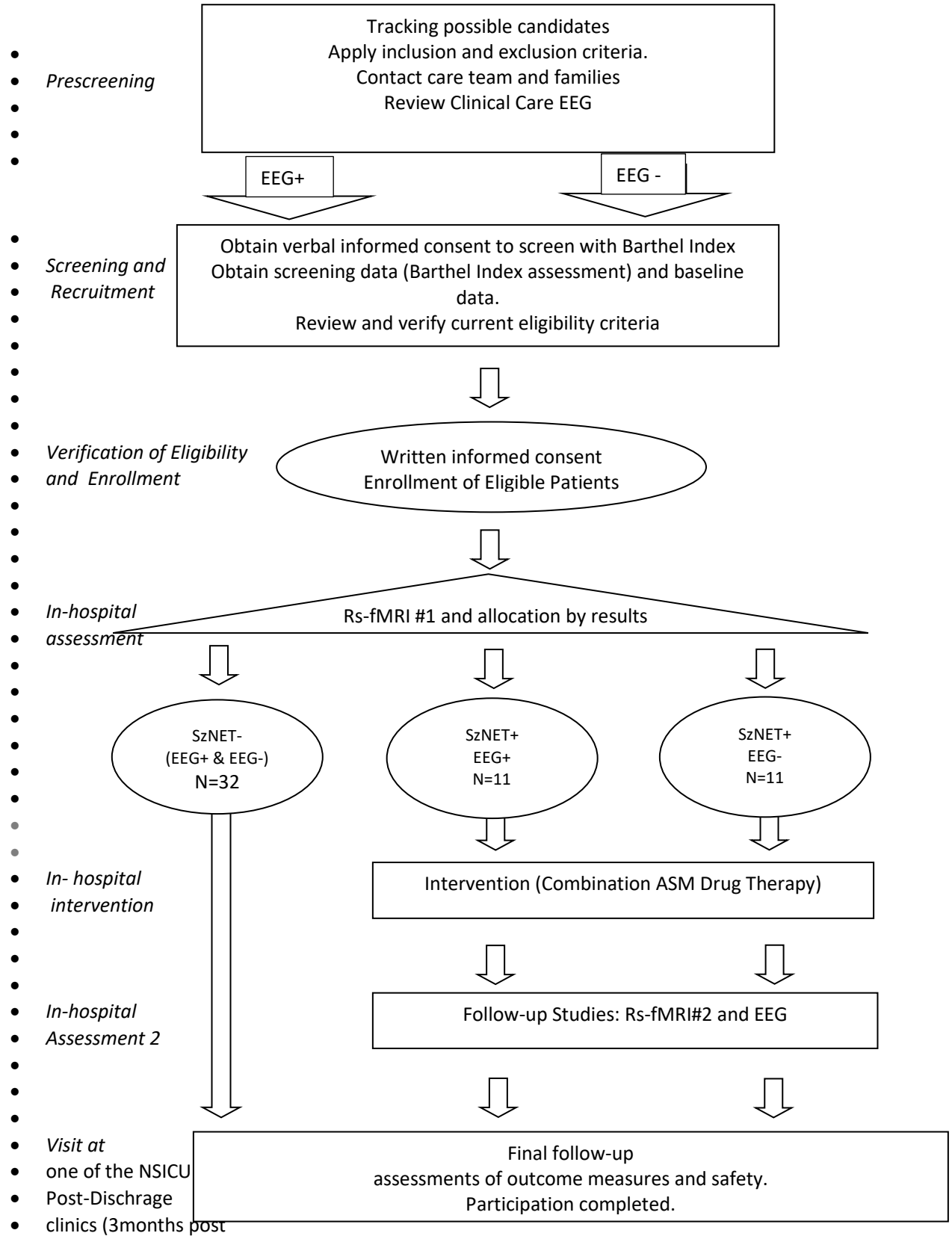
End-of-study criteria or stopping-rules for the entire study.

If a severe adverse event related to study participation occurs (e.g., transportation to the MRI scan, side-effect of the ASM intervention), the study will be suspended pending review by the IRB and implementation of an approved Corrective and Preventative Action Plan.

Based on pilot data, SzNET is common in patients who are EEG+, but only present in about 30% of patients who are EEG-. After enrolling 40 patients, we will review the results of rs-fMRI #1, and the study will stop because of futility if we observe one the following criteria:

- SzNET are detected in less than 70% of the patients classified as EEG+ or less than 10% of the patients in the EEG- group.
- More than 50% of the subjects from the intervention group do not show a change in SzNET after the study treatment.

Figure 2. Study Flow Diagram.



4.1.Treatment Design

The intervention and its compliance criteria are defined as receiving treatment by minimum 72 hours since loading dose start time or up to ten complete days with administration of two of the following ASM regimens:

Phenobarbital:
Pediatric population
Loading dose 20 mg/kg intravenous. Max dose 1000mg
Maintenance dose 4mg/kg/day. Max dose 300mg/day.
Adult population
Loading dose 20 mg/kg intravenous.
Maintenance dose 4mg/kg/day. Max dose 600mg/day.

Levetiracetam
Pediatric population
Loading dose 60 mg/kg intravenous. Max dose 4000mg.
Maintenance dose 40mg/Kg/day, Max dose 3000mg/day intravenous or enteral.
Adult population
Loading dose 60 mg/kg intravenous. Max dose 4500mg.
Maintenance dose 1500mg to 4000mg/day intravenous or enteral.

Lacosamide
Pediatric population
Loading dose 10 mg/kg intravenous, Max dose 400mg.
Maintenance dose 4mg to 8mg/Kg/day. Max dose 300mg intravenous or enteral.
Adult population
Loading dose 200mg to 400mg intravenous
Maintenance dose 200-400mg/day intravenous or enteral.

Valproate
Pediatric population
Loading dose 30mg/kg intravenous. Max dose 3000mg
Maintenance dose 20mg to 30mg/Kg/day, Max dose 3000mg/day.
Adult population
Loading dose 40 mg/kg intravenous. Max dose 3000mg
Maintenance dose 15-30mg/Kg/day, Max dose 3000mg/day.

Phosphenytoin,
Pediatric population
Loading dose 20 mg PE/kg intravenous. Max dose 1500mg PE
Maintenance dose 4mg PE/Kg/day. Max dose 300mg PE/day.
Adult population
Loading dose 20 mg/kg intravenous. Max dose 1500mg PE
Maintenance dose 4-7mg PE/Kg/day. Max dose 400mg PE/day

All maintenance doses are given every 12 hours, starting 12 hours after the loading dose.

Participants with GCS 9 to 12 will not receive phenobarbital as one of the intervention ASM, and the loading dose of one of the two selected ASMs will be omitted.

All patients with an identified SzNET in rs-fMRI#1 will be included in the intervention group. Within one and six days after the first scan, the care team will decide and start the intervention with two ASM agents from the list. The intervention phase occurs between rs-fMRI#1 and the day of follow-up rs-fMRI#2 and repeated EEG. The intervention is considered complete and the follow-up tests can be done if the patient received the study ASM for at least 72 hours after the loading dose start, and the second scan must be done within 72 hours of the last intervention ASM dose. The treatment protocol can continue up to a maximum of ten days to improve the opportunity to schedule the scan. Thus, the rs-fMRI #2 must be done at a time between 73h and 312h (the fourth and thirteenth days) after the intervention phase starts, and the subject can still be receiving the intervention at that time.

Once the rs-fMRI #2 is obtained, the subject's ASM treatment can be continued or changed for clinical reasons depending entirely on the care team's decision, then it will not be considered part of the study's intervention phase or be related to the research team.

The intervention aims to validate the epileptogenic background of the SzNET by using an ASM that is known to be effective. We expect the intervention will influence the improvement of the SzNET. We hypothesize that the intervention will selectively modulate the networks caused by epileptogenic activity, while having less to no impact on abnormal networks caused by other phenomena.

The length of the intervention is designed to be adequate for pharmacological modulation of epileptogenic activity. The six-day time frame between the minimum and the maximum treatment protocol time facilitates a window for the rs-fMRI schedule that is a realistic schedule time frame in the ICU.

From the different ASM options the key intervention and first option to be considered as intervention will be phenobarbital + levetiracetam. This specific ASM combination will be communicated clearly to the ICU care teams as the first line of the study intervention. However, for clinical reasons the care team will be free to select any combination of two or more study listed ASM regimens. On day two of maintenance dosing, the phenobarbital serum level will be measured if it is one of the selected medications, and a new loading dose will be given to aim for a level of 40mcg/ml.

The dual ASM loading dose approach is designed to increase the likelihood of a timely response to SzNET, as compared to using only one ASM and its rational use is supported by the better response suggested in Status epilepticus[23,24]. With a gentler medication regimine of single agent, given the data, should be less likely to see an impact on the SzNET. If we go this route and we don't see an effect, then we are also unlikely to get any further funding to repeat such a study with dual agent, given the competitive nature of grant application and the clinical team may also loose appetite for supporting more studies.

Phenobarbital is included specifically because of its high efficacy in treating epileptogenic activity[25,26]. Phenobarbital can cause ventilatory depression. However, the patients with SABI during the study timeframe are expected to be intubated with good airway and ventilatory control, and thus less likely to require significant escalation of airway or ventilatory support. Furthermore, all ICU patients are monitored with all necessary safety considerations for airway management and ventilation. ASM maintenance dosing can be modify by the care team during the intervention phase and still be compliant, as long as the dose remain equal or higher than the minimum dosage stated in the insert. The care team may adjust ASM based on clinical determinants after the second rs-fMRI without compromising the protocol, as the main outcome measures are based on data collected on that day.

The short term-use of dual ASM that we would be giving to patients with suspected non-convulsive status epilepticus or subclinical seizures with coma in the ICU is off-label because the intervention is not given to treat confirmed seizures by their standard definition. However, the possibility of deleterious epileptogenic activity cannot be discarded in the eligible patients and the routes of administration and concomitant dosage levels are appropriate for status epilepticus (see appendix B to F), not increasing the risk of the intervention compare to the regular use of the listed ASM. The study's intervention does not significantly increase the selected subjects' risks leading to a discouraging risk-benefit relationship because these subjects are already at very high risk of death if they do not wake up from their coma. Thus, any opportunity to try to improve the chances of waking up from coma is worth

the risk of the antiseizure medication. That risk benefit relationship is the reason why empiric antiseizure medication is often given in SABI patients with DoC.

Participants with a GCS of 9 to 12 are at lower risk compared to those with a GCS of less than 9 and may not require ventilatory support. To maintain a favorable risk-benefit ratio for their participation, these participants will not receive phenobarbital as one of the intervention ASM, and the loading dose of one of the two selected ASMs will be omitted.

The present study and its results are not intended to try to support changes in the indications, the labeling or the advertising of medical devices use or drugs. The study's informed consent will describe the purpose and the procedures and interventions described in this trial. Taking into account the statements in this protocol we are not submitting an FDA " Investigational New drug Application (IND)" because according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

i. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

ii. it is not intended to support a significant change in the advertising for the product;

iii. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

iv. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; (revision by the IRB and compliance with the protection of human subjects)

v. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

vi. it does not intend to invoke 21 CFR 50.24.[29]

4.2. Experimental Design

This pilot study is a stratified interventional study that will evaluate the response of an exploratory biomarker. There will be no placebo-controlled groups, and the study main intervention will be systematically assigned to all subjects with SzNET identified by the first rs-fMRI. Patients without SzNET will not receive the study treatment and will continue their medical therapy as directed by their care team. They will be included in the required analysis for aim 2 and 5. Two specialists will assess the two post-intervention follow-up studies, the rs-fMRI#2 and the repeat EEG, providing the only blinding needed. These study design elements will ensure the technical requirements necessary to calculate the sample size required for a larger trial in EEG-negative patients with SzNET-positive and explore two important aspects of the biomarker SzNET: its correlation with the EEG response of patients and the effect size of its response to the intervention ASM.

4.3. Measurement Design

Table 2. Variables of interest: their occasions of evaluation, their uses for the aims, their roles in the study

Variables within Domains	Scale[1]	Occasions[2]	Aims[3]	Main Roles
Identifiers				
Participant's unique ID	nominal	all	all	identifier

Intervention	categorical	E	All, except aim 2	intervention
Clinical Health Profile				
Spontaneous ventilation	Binary	E, 2	Aim 1	Exploratory uses
Glasgow Coma Scale (GCS)	Ordinal 3-15	S, E, 2	--	Screening
weight	kg	E	--	dosing
height	cm	E	--	dosing
body mass index (BMI)	kg/cm^2	E	--	dosing
body surface area (BSA)	kg/m^2	E	--	dosing
Supratentorial decompressive craniectomy	Binary	S, E, 2	--	Exploratory uses
age	decimal yrs	S	--	screening
sex	categorical	S	--	Exploratory uses
Pre-MSABI BIS (appendix a)	Ordinal 0-100	S	--	screening
Medical Records				
Presumed etiologies of disorder of consciousness	Categorical	S	--	screening
co-morbidities list	nominal	S	--	screening
Clinical tests				
2HELPS2B Score	Ordinal 0-7	S	--	Exploratory uses
pre-intervention EEG status (EEG monitoring Seizures)	Binary	E	All	classification
Research tests				
SzNET presence	Binary	E	All	Classification and primary outcome
Total Volume (TV)	continuous	2	Aim 1a	primary outcome
Total Volume Reduction (TVR)	continuous	2	Aim 1a, 3, 4	primary outcome
Power Spectrum (PS)	continuous	2	Aim 1b	primary outcome
Power Spectrum Improvement (PSI)	continuous	2	Aim 1a, 3, 4	primary outcome
Typical RSN improvement	Binary	2	Aim 4	Secondary outcome
EEG improvement	Binary	2	Aim 3	Secondary outcome
Protocol Time Frames				
Days of antiseizure medication	Days (discrete)	2	-	Confounder
Time from MSABI to rs-fMRI#1 (days)	Days (discrete)	2	-	Confounder
Time from MSABI to rs-fMRI#2 (days)	Days (discrete)	2	-	Confounder
Time from MSABI to treatment protocol start (days)	Days (discrete)	2	-	Confounder
Time from enrollment to rs-fMRI#1	Days (discrete)	2	-	Secondary outcome
Questionnaires/survey instruments[4]				
Anxiety: PROMIS Emotional Distress—Anxiety—Short Form (appendix H)	Ordinal 7-35	3	Aim 5	Exploratory outcome

Depression: Neurological Disorders Depression Inventory for Epilepsy (NNDI-E) (appendix I)	Ordinal 6-24	3	Aim 5	Exploratory outcome
Quality of Life: QOLIE-10-P (appendix J)	Ordinal 1-10	3	Aim 5	Exploratory outcome
Telephonic Montreal Cognitive Assessment (appendix K)	Ordinal 0-15	3	Aim 5	Exploratory outcome
ASM toxicity: Liverpool adverse event profile test (appendix L)	Ordinal 19-76	3	Aim 5	Exploratory outcome
Safety Monitoring		Any time (AT) After E		
Adverse event related with the transportation to the MRI scan.	Ordinal 1-5	AT after E	-	safety monitoring
Adverse event related with the transportation to the MRI scan. Description	nominal	AT after E	-	safety monitoring
Adverse event related with the intervention	Ordinal 1-5	AT after E	-	safety monitoring
Adverse event related with the intervention. Description	nominal	AT after E	-	safety monitoring
Dropout	binary	AT after E	Aim 6	Secondary outcome
Dropout date	ordinal	AT after E	Aim 6	Secondary outcome
Dropout cause	nominal	AT after E	-	safety monitoring
Feasibility				
Informed consent acceptance	Binary	E	Aim 6	confounder

[1] Units of measurement or the scale.

[2] Occasions of evaluation or retrieval: **S** = screening, **E** = enrollment, **2** = rs-fMRI#2, **3** = 3 months

[3] The specific aims in which the variable will play a role in data analyses.

[4] will be collected by one of the NSICU Post-Discharge clinics.

In Table 2, the treatment regimens must include two from:

6. Phenobarbital
7. Levetiracetam
8. Lacosamide
9. Valproate
10. Fosphenytion

In Table 1, the allowed Presumed etiologies of disorder of consciousness are:

1. Hypoxia/anoxia (i.e., respiratory arrest with preserved circulation)
2. Hypoxic-ischemic injury (i.e., cardiac arrest).
3. Ischemic stroke.
4. Intracerebral hemorrhage.
5. Subarachnoid hemorrhage.
6. Subdural hemorrhage
7. Epidural hemorrhage
8. Traumatic brain injury (penetrating).
9. Traumatic brain injury (non-penetrating).
10. Venous sinus thrombosis/cortical vein thrombosis

Baseline Variables:

- The Medical record domain variables will focus on retrieving information to screen patients and verify inclusion-exclusion criteria. Thus, the previous history of epilepsy and neurological problems that could lead to functional dependence greater than expected for age are relevant confounders that will be avoided in this pilot trial. The presumed etiology of DoC are the inclusion criteria, and we expect to evaluate the rs-fMRI for exploratory purposes in subgroup analysis. Glasgow coma scale GCS is a baseline variable that will be collected in more time points.
- The presence of SzNET will classify the patients that will receive intervention corresponding to the protocol and those that will only continue medical treatment according to care team indications in case of the presence or the absence of SzNET in the first MRI, accordingly. Outcomes will be reported as proportions and differences of proportions of patients with SzNET among EEG- and EEG+.
- Surface EEG monitoring pre-intervention (Seizures) is a binary variable collected from the total available surface EEG monitoring before rs-fMRI#1 with EEG+ and EEG- as possible values and retrieved by the investigators from the medical record or direct communication with the Epileptologist, which later must be supported in the medical records. EEG+ is defined as surface EEG with the presence of electrographic seizure, electroclinical seizure or ictal-interictal continuum.

Outcome Variables:

Each SzNET is made of one or more BOLD signal independent components that share atypical temporal or spatial features [11].

- SzNET total volume (TV) is the sum of the volumes of the SzNET independent components. The TV change from before to after the intervention is a ratio expressed as the TV reduction (TVR), and is given by:

$$TVR = 1 - \frac{\sum_{i=n}^{n} P_i}{\sum_{i=n}^{n} E_i}$$

Where P is the volume of a post-treatment SzNET, E is the spatial volume of an initial SzNET and n is the amount of SzNET in each rs-fMRI.

- Power Spectrum (PS) is the sum of the power spectrum of the SzNET independent components normalized by their spatial volumes. The PS change from before to after the intervention is a ratio expressed as the PS improvement (PSI) and is given by:

$$PSI = 1 - \frac{\sum_{i=1}^{n} [P \int_{6.78}^{27.12} f(s)]_i}{\sum_{i=1}^{n} [E \int_{6.78}^{27.12} f(s)]_i}$$

Where F(S) is the power spectrum curve.

- EEg improvement Binary variable categorized in "with improvement" or "without improvement", obtained by expert's overall qualitative assessment comparing the follow-up study EEG and the clinically indicated EEG considered at the enrollment time. This qualitative assessment will be based on the EEG's background and the presence of electrophysiological signs of ictal or interictal activity.
  These signs are described by the American Clinical Neurophysiology Society as:
  - Epileptiform Discharges
  - Rythmic and periodic patterns
  - Electrographic and electroclinical seizures.
  - Ictal-interictal continuum.

  It will be used to investigate the association in patients with a clear improvement of their SzNET. Such improvement will be defined as more than 0.5 TVR or 0.5 PSI threshold.
- RSN improvement is a binary variable collected by the study coordinator based on clinical records of the rs-fMRI#2, taking into consideration the spatial and temporal features and the number of canonical RSN

observed in the rs-fMRI#2. It will be used to investigate association in patients with a clear improvement of their SzNET; such improvement will be defined as more than 0.5 TVR or 0.5 PSI threshold.
- All the variables listed as exploratory will be studied for association in patients with clear improvement of their SzNET, such improvement will be defined as more than 0.5 TVR or 0.5 PSI threshold.
-

Comments regarding extended age range: 18 months to 70 years of age had heterogeneity of brain function related to both neurodevelopment and old-age related degenerative processes. However, the impact of seizure on brain networks that causes suppression of consciousness is similar through these age groups. For example when seizure occurs we expect reduction in consciousness in both young and old who have either epilepsy or acute brain injury. Patient's age may have impact on the clinical outcomes and connectivity aspects of resting state networks, for that reason we will analyze seizure networks (SzNET) different to the typical resting state networks (RSN). The analytical approach to SzNET that depend mostly on the ictal activity will be quantitative, but RSN improvement is a binary variable based on experts opinion judging the presence or absence of these normal networks that are described and used for neuroprognostication across different age groups[30-32]

Safety and Feasibility Variables:
These variables will be collected as part of the safety monitoring. Some of these variables also aim to determine how practical and viable is the study design, recruitment strategies, and participant retention in our institutional actual context. By closely monitoring the enrollment rate, which measures the efficiency of the recruitment process, and the dropout rate, which indicates the probability of the participants to continue with the study. Valuable insights can be gained regarding the feasibility of conducting a similar study on a larger scale. This findings will provide crucial information for refining future study protocol and improving recruitment and retention strategies to ensure the successful implementation of future research projects with similar conditions.

5. Study Participants

5.1. Numbers of Participants

5.1.1. Number to be screened: N=68

5.1.2. Number to be enrolled: N = 54

Rationale of Number Expected to be Screened:

The Study will employ a quota sampling method to enroll four groups of patients, designated as: SzNET+/EEG+, SzNET+/EEG-, SzNET-/EEG+, and SzNET-/EEG-. Importantly, only the two SzNET+ groups have a minimum enrollment goal. Thus, enrollment will stop once each of the two SzNET+ groups enroll ten patients. The logic behind the patient screening and enrollments is as below.

1. SzNET+/EEG- Strata: To successfully complete the study treatment in 10 EEG- subjects, who would eventually be found to be SzNET+, we need to enroll 11 subjects, as we anticipate a 1 in 10 subject attrition. In our preliminary SABI data (Fig 2), of those who would meet inclusion/exclusion criteria, 30% with EEG- were SzNET+. Thus, we expect to need to enroll approximately 37 EEG- patients with completed good quality studies. Lastly, due to the ICU environment and the Barthel score required, we expect 80% of the subjects eligible for enrollment, thus 46 EEG- patients will be screened to fulfill this group's recruitment goal.

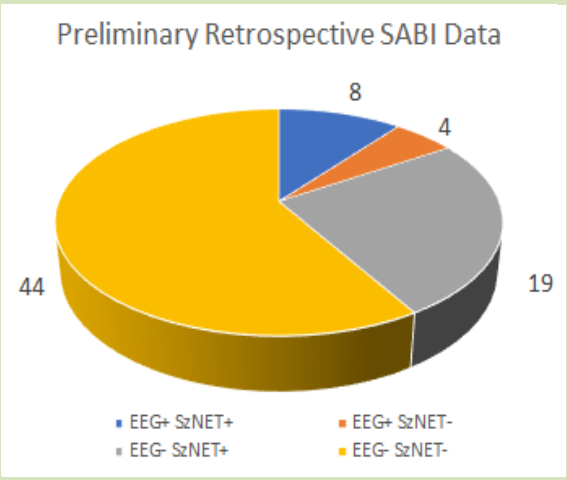


Fig. 1. Adult and Peds SABI EEG and Seizure Network (SN) prevalence (N=63). EEG-SN+ comprise 30% of the SABI population.

2. SzNET+/EEG+ Strata: To successfully complete treatment in 10 EEG+ subjects, who would eventually be found to be SzNET+, we need to enroll 11 patients, as we anticipate a 1 in 10 subject attrition. In our preliminary SABI data (Fig 2), of those who would meet inclusion/exclusion criteria, 67% of the EEG+ were SzNET+. Thus, we expect to need to enroll approximately 17 EEG+ patients with completed good studies. Lastly, due to the ICU environment and the Barthel score required, we expect 80% of the subjects eligible for enrollment. Thus, 22 EEG+ patients will be screened to fulfill this group's recruitment goal.

Participants who drop out, are withdrawn, or have missing data will not be replaced until second aim's data is complete, afterwards we will continue recruitment until we meet the two strata proposed enrollment. The subjects analyzed for the second aim will only include those scanned until the time when the first group of SzNET+/EEG+ or SzNET+/EEG- recruitment will be completed. By this strategy, the initial estimate of the proportion of SzNET+ subjects by EEG subgroup could be less biased, and we will guarantee the required number of subjects to start the interventional phase of the study while optimizing the total amount of initial rs-fMRI needed.

Sources of recruitment: UNCH PICU, NSICU, SICU, CTICU, CICU or MICU patients meeting study inclusion and exclusion criteria. Potential research subjects will be identified by the study team members chart screening of all the patients with EEG orders from ICU, for eligibility.

Interventional Study numbers of enrollees expected to receive the treatment regimen: Since this is a non-controlled interventional open-label pilot study, and we need a total of 20 subjects successfully to receive the study therapy AND repeat rs-fMRI, then due to intra-study attrition of 1:10, we expect to treat a total of 22 patients with the study therapy.

5.2. Eligibility Criteria

This study will be done in moderate to severe acute brain injury (MSABI) patients aged 18 months to 70 years, at risk of epileptogenic activity and presenting with coma. The target population is recruited at Pediatric ICU (20 beds) and the Neuroscience ICU (22 beds) from UNC health at Chapel Hill, which acts as a tertiary referral center for patients from North Carolina and surrounding states. The Pediatric ICU treats an average of 109 patients/year with primary ICD codes for traumatic brain injury, arrest and encephalopathies & coma, which are the main codes for the target population.

In the United States, 795,000 people experience a stroke (ischemic or hemorrhagic) every year[33], and TBI causes approximately 282,000 hospitalizations and about 56,000 deaths each year [34]. SABI from TBI, stroke, and other neurological problems require treatment in the ICU, where the incidence of Seizures is approximately 35%[5,35].

5.2.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Age from 18 months to 70 years at ICU admission by medical chart review.
- Suppression of consciousness related to a neurological injury by medical chart review.
- GCS less than 13 at enrollment.
- Diagnosis of Acute brain injury by TBI, hypoxic-ischemic insult, cardiac arrest or stroke by medical chart review.
- 2 to 90 days from acute brain injury to enrollment time by medical chart review.
- Have a routine clinical surface EEG performed after the admission to PICU, NSICU, SICU, CTICU, CICU or MICU.
- Clinically stable to undergo MRI scan, This stability is defined by care team concept, which should be stated in the medical records.
- Hospitalized in NSICU, PICU, SICU, CTICU, CICU or MICU

5.2.2. Exclusion Criteria

Any individual who meets one or more of the following criteria will be excluded from participation:

- Previous medical history of Epilepsy by medical chart review.
- Previous medical history of neurological conditions that lead to dependence on care for basic daily activities, by BIS less than 80, examined with the patient's LAR at the time of the in person interview for obtaining the informed consent. If there is medical history of neurological conditions with concerning for impaired independence and the functional status of the patient cannot be addressed properly the patient will be excluded from participation.
- Known allergy/Hypersensitivity or medical contraindications (like porphyria or cardiac arrhythmias) to the treatment protocol options, leaving no potential combination of drugs for the intervention without concerns for adverse events related to known preexistent conditions.
- Considered with Brain death by the care team in the medical record, at any time.
- Is following Commands in 3 different exams from at least 2 different providers**.**
- Contraindications for MRI scan.
- Prisoner human subjects by medical chart review.
- Confirmed currently pregnant by medical history or by positive blood or urine pregnancy test done in the present hospital admission.
- Treating physician determines the patient is no candidate to receive 2 of the 5 protocol-specified ASM.

5.3. Enrollment/Selection Strategies

5.3.1. Prospective Recruitment

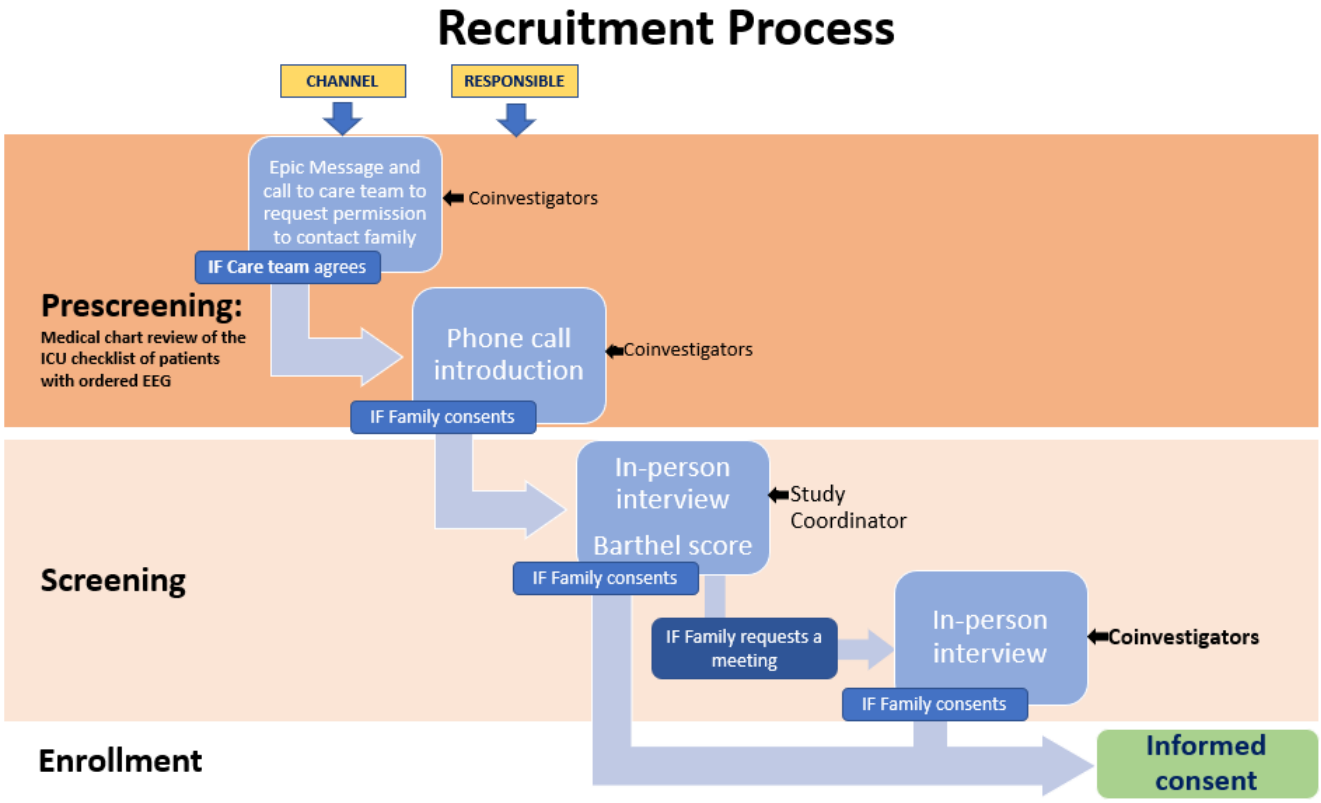
The recruitment for this study is based on three steps as shown in Figure 3. The initial prescreening does not imply additional activities to the standard of care and is designed to provide an opportune identification of potential research subjects while they are stable enough to meet the inclusion criteria. The screening period is planned to be short with the application of one additional screening test before enrollment and driven by interaction between the research team and the legally authorized representative (LAR) of the research subject.

By enrollment criteria, the patients from the target population for this study are not able to give consent on their own. Thus, the LAR will be in charge of giving consent on behalf of all the human subjects, including the children. The particularly vulnerable populations of pregnant subjects and prisoners will be excluded from the study. In the particular case of pregnant subjects they will be excluded due to higher risk of study-related pregnancy complications.

Relevant aspects regarding the protection of particularly vulnerable subjects: This research is considered to involve greater than minimal risk but presents the prospect of direct benefit to the individual subjects, thus in the case of children, the consent of one of their parents will be required.

Language recruitment barriers: Informed consent form in Spanish, and Spanish-spoken in-person interview and phone calls by study personnel will be an available alternative for the non-English speaking population that might prefer Spanish to reduce language recruitment barriers.

The recruitment strategy process is described in Figure 3.



5.3.2. Screen Failures

We expect less than 5% of potential subjects will be screen failures because individuals will be screened and enrolled on the same day. That is possible because most of the eligibility criteria will be previously reviewed during the prescreening process. The only screening test is the application of the Barthel Index, which will be done after verbal consent for screening at the time of the in-person interview for the study informed consent. At that time, the screening list will be complete, and the final decision of eligibility for enrollment will be taken before asking for informed consent for the study. Patients deemed ineligible during the interview will not be able to re-screen.

5.4.Strategies for Retention

The primary strategy to prevent dropout during the treatment phase is to keep frequent direct communication with the care team to schedule rs-fMRI #2 as soon as possible by the indicated time frame.

The average SABI patient volume treated last 3 years at the NeuroICU and the PICU at UNC health was 1238 and 109 patients/year respectively (via UNCH operation analyst), for which an adequate volume to cover enrollment is

expected. UNC health has previously enrolled MSABI patients on research and has all the necessary equipment and resources to complete the eligibility evaluations for this study.

5.5. Matching and Stratification

In ICU patients with suppression of consciousness, we will use the routine care EEG to stratify patients into two groups, EEG+ and EEG- during the prescreening. EEG+ will be defined by either electrographic seizure, electroclinical seizure or ictal-interictal continuum as defined by the American clinical Neurophysiology Society's Standardized Critical Care EEG Terminology[28], whereas EEG- will be lacking these features. EEG in this protocol does mean continuous video EEG, which is the stand of care for UNCH ICU patients.

To select the patients for screening and enrollment, we will use a quota sampling strategy. Specifically, we will recruit eleven SzNET+ patients consecutively for each EEG+ and EEG- group. Once one of those group's enrollment is complete, we will continue screening only patients from the EEG category that could be enrolled in the incomplete SzNET+ group.

As this is a pilot study, including a wide range of age, the study design does not include matching.

5.6. Randomization and Concealment

This is an open label, nonrandomized study. Not applicable.

5.7. Blinding

The Follow-up EEG will be assessed by an epileptologist blinded to rs-fMRI#2 results. Those results will not be posted in the medical records or commented with personnel outside the clinical rs-fMRI service until the follow up EEG and its comparison results should be collected. This blinding doesn't need to be removed to reassure the patient SOC.

6. Treatment Design: Procedures

Description For this uncontrolled, open-label, interventional trial, the intervention will be assigned to all enrolled patients with SzNET+ by the first rs-fMRI. The intervention and its compliance criteria are defined as receiving treatment for three to ten complete days with at least two of the following ASM regimens, simultaneously:

1. Phenobarbital 20 mg/kg intravenous loading dose
2. Levetiracetam 60mg/kg intravenous loading dose
3. Lacosamide 200 mg intravenous loading dose
4. Valproate 30 mg/kg intravenous loading dose
5. Fosphenytion 20 mg/kg intravenous loading dose

All the maintenance dose regimens will start the next day to loading dose, and dosing wil be calculated for weight and age of both medications within the combination group, until the repeat rs-fMRI. As soon as possible, the research team will inform the care team that the patient has been allocated to the intervention branch so they can decide on two ASM regimens from the previous list to start the treatment. On the same day, the research team will confirm by medical charts the two ASM selected and the date and the time of the first loading dose infusions. The intervention phase takes the time between rs-fMRI#1 and follow-up rs-fMRI and EEG. The rs-fMRI#2 must be performed after at least three complete days of treatment and no later than eleven days after the beginning of the intervention phase, but in case of ASM withdrawal, the rs-fMRI#2 must be done no later than 72 hours from the last dose. As outcome measures are based on data collected the day of the second rs-fMRI, after that day, the care team will be free to adjust ASM according to what better fits the patient without compromising the protocol.

The study's main intervention option consists of the Phenobarbital and Levetiracetam regimens. However, the clinical team can select any combination of two or more ASM regimens from the list provided, for clinical reasons. On day two of intervention, the phenobarbital serum level will be measured if it was one of the selected medications, and a new loading dose will be given to aim for a serum level of 40mcg/ml.

Participants with GCS 9 to 12 will not receive phenobarbital as one of the intervention anti-seizure medications (ASM), and the loading dose of one of the two selected ASMs will be omitted. For these participants the study's main intervention option consists of the Levetiracetam and Lacosamide regimens, omitting the Lacosamide loading dose.

Rs-fMRI schedule (Day 0-1 of Enrollment)

- Order Pre-Intervention research-related rs-fMRI#1

Time from enrollment to intervention start (Days 1-6 of Enrollment)

- Scan **should** be performed within 3 days **from enrollment.**
- **To undergo any study indicated rs-fMRI, the participant should not have been diagnosed with vasospasm based on their most recent transcranial Doppler examination, conducted within the last 3 days.**
- The time frame between fMRI scan and intervention start will range from 1 to 6 days.
- Obtain (research driven) fMRI
  - What is rs-fMRI
    - MRI generates images based on the interaction of the body with potent electromagnetic fields.
    - Rs-fMRI uses BOLD signal to identify vascular reflexes related to neuronal activation.

- What is the process of transporting the patient to the fMRI?
  - As SOC at UNC Health, a transport team made of two nurses, one fellow physician and one respiratory therapist gathers with the patients at ICU and checks to have the required equipment for transportation.
  - The subject is transported by the transport team from the ICU to the MRI Scan within the hospital, located on the first floor or the basement of the same ICU building, according to the MRI scanner availability.
  - Once the rs-fMRI scanning is acquired the transport team transports the subject back to the ICU.
- How long does the fMRI routinely last?
  - Around 25 minutes for the scanning
  - Variable transportation times, from ICU to scanner and from scanner to ICU
- What are the risks associated with the fMRI?
  - Patients meeting eligibility criteria do not have risk of adverse events related to the electromagnetic fields
  - Rs-fMRI does not require contrast agents to be administered.
  - In case of tattoos with suspected high levels of ferromagnetic compounds cold compresses can be apply to prevent heating.
  - Transportation through the hospital to perform the MRI scan can be associated with mechanical risks and support devices malfunction. Trained personnel is in charge of the process, which is supervised by a physician.

- SzNET Stratification of rs-fMRI
  - SzNET (-): with EEG (+) or EEG (-).
    - N=32
    - No protocol Intervention-driven, combined ASM is administered.
    - They will not receive the second fMRI.
    - They will only be followed at the 3 months post discharge visit if they are scheduled to one of the NSICU Post-Dischrage clinics.
    - MRI scan transportation related AE Review.
  - SzNET(+): with EEG(+).
    - N=11
    - Proceed with combined ASM Intervention.
    - Intervention **must** start within 1 to 6 days after enrollment.
    - AE Review.
  - SzNET(+):with EEG(-)
    - N=11
    - Proceed with combined ASM Intervention.
    - Intervention **must** start within 1 to 6 days after enrollment.
    - AE Review.
- Study team will inform the family of the rs-fMRI results and upload the official report to EPIC.

Intervention start (Days 1-6 from Enrollment)

- **Clinical Care Team** will choose the intervention regimen.
  - If participant was already on **two** of the protocol-approved ASM, the participant will be required to start the intervention by administering the protocol-driven loading dose infusions outlined for

each of the combined ASMs, or by administering the loading dose for any of the other 5 listed ASM options. A third option in this case is to administer protocol-driven loading dose of one of the current medications and add another of the 5 ASM loading dose and maintenance regimen.
    - If participant was already on **one** of the protocol-approved ASM, the participant will be required to start the intervention by administering the protocol-driven loading dose outlined for the ASM that the participant was previously receiving *along with* another protocol-driven ASM loading dose from the ones listed on the protocol.
    - If participant **was not receiving any** of the protocol approved ASM, the participant will be administered a loading dose of two of the 5 protocol approved ASM.
    - If the clinical care team does not want to use a combination of two of the 5 protocol-approved ASMs, they will not be enrolled into the study.
- **Reasearch Team** will
    - Review adverse events
    - Review participant medical record to confirm which combined ASM was decided by the clinical care team and charge it into EPIC.
    - Document date and time of first intervention-related loading dose infusions.

Maintenance Dose (Up to 3 to 10 Days from loading dose start)

- **Research Team** will charge to EPIC the maintenance doses and verify ASM Administration**.**
    - The maintenance protocols must be administered for at least 72 hours from the start time of the loading dose infusion.
    - The MD can continue for up to 10 days while the second fMRI is trying to be scheduled and obtained.
    - The ASM can be continued beyond 10 days but would no longer be considered in the protocol-driven intervention phase.
    - The Post-Intervention assessment scans can be obtained, even if the participant remains on ASM beyond the maintenance dose period.
    - **To undergo any study indicated rs-fMRI, the participant should not have been diagnosed with vasospasm based on their most recent transcranial Doppler examination, conducted within the last 3 days.**
    - If one of the combined doses administered is phenobarbital
        - *On Day 2 of the MD:*
            - Specimen Collection (phenobarbital serum level UNC Hospitals Test ID LAB30) will be ordered by the research team.
            - The **research team** reconvenes the maintenance dosing with the **medical care team** to aim for a level of 40mcg/ml.
    - Review any AEs associated with ASM
    - Review Dropout data (if applicable)
- **Medical Care Team** will decide if the patient continues with the study's antiseizure medication regimens. In this case, they will continue to provide the medication, and thepatient will be responsible for expenses.

Acquisition, storage and preparation: The present study does not employ experimental compounds, all the medications related to the study follow the same standard Storage rules of the medications regularly used at the ICUs of UNCH.

Administration: IV and enteral administration with infusion times and observation according to the internal protocols for each medication at the patient's corresponding ICU.

Rescue Procedures/Medications

- If emergent adjustments to the treatment plan are needed those will be decided by the care team.
- Administration of additional ASM to the study intervention is allowed as determined by the clinical team.

Adherence Monitoring/Evaluations the intervention's ASM timing and dosing will be checked from the medical charts. On day two, the phenobarbital serum level will be measured if it was one of the selected medications, and a new loading dose will be given to aim for a serum level of 40mcg/ml.

Concomitant Therapies There are no prohibited or recommended concomitant therapies. Calcium channel blockers must be used with precaution when administering some of the protocol ASM (see appendix B & E).

Follow-up tests (Days 3-13 from Start of Loading Dose)

- Order Post-Intervention research-related rs-fMRI (#2)
    - Scan must be **performed** after completing a minimum of 72h of intervention ASM protocol (including loading and maintenance doses).
    - Scan must be **completed** within 72hrs of last intervention ASM dose.
    - **To undergo any study indicated rs-fMRI, the participant should not have been diagnosed with vasospasm based on their most recent transcranial Doppler examination, conducted within the last 3 days.**
    - Post scan, the participant can continue on their current ASM regimen or be changed based on routine clinical care decisions.
    - The official results repport will be uploaded to EPIC after the post-intervention research-related EEG has been reported.
    - AE Review:
    - Review Dropout data (if applicable)
    - Collect GCS Score
- Obtain Post-Intervention research-related EEG
    - EEG characteristics
        - The EEG is a non-invasive medical test with very low risk of adverse events. Very rare complications could be associated with skin reactions to the conducting material used for the electrodes and malfunction of the device.
        - Bedside monitoring.
        - Minimum 1 hour run.
        - Without Photostimulation.
    - EEG recording must be obtained within 72hrs of last intervention ASM dose.
    - Post the EEG, the participant can continue on their current ASM regimen or be changed based on routine clinical care decisions.
    - EEG will be reviewed by a blinded epileptologist for rs-fMRI (#2) results.
    - For ethical reasons the results will be shared with the care team.

7. Schedule of Activities and Procedures

7.1.Table of Events

Procedure		ICU Range days Since MSABI event (-1 to -90) prescreening	Screening/Enrollment interview (Must be stable to transport and scan)	Study baseline (Time frame from enrollment, 1 to 3 days)	Intervention Phase Between rs-fMRI #1&#2 (Time frame from enrollment, 1 to 16 days)	Follow up Studies RANGE study day: Between 3th to 13th of the intervention start (Time frame from enrollment, 3 to 19 days)	One of the NSICU Post-Dischrage clinics At 3 Months from discharge
Recruitment	Eligibility assessments by medical chart review	X	X				
	Informed consent		X				
	Enrollment and rs-fMRI Schedule		X				
	Allocation			X			
Patient or LAR surveys	BIS Pre-MSABI		X				X
	NDDI-E						X
	PROMIS emot. Dist. - Anxiety – Short form						X
	Liverpool AEP						X
	QOLIE-10-P						X
	MoCA						X
Treatment	Study protocol treatment				X*		
	Standard care treatment	X	X	X	X	X	X
Physical Exams	Glasgow Coma Scale	X	X	X		X*	
	Neurological exam						X
Safety Monitoring	Review of adverse events reported.				X	X*	
Clinical tests	Pregnancy test	X					
	Surface EEG	X					
Research tests	Rs-fMRI			X		X*	
	Follow-up EEG					X*	
	Phenobarbital serum levels				X*		

*Activities including only SzNET + patiens.

7.2. Screening

Patients meeting eligibility criteria will be followed by the research personnel to check with the care team the time when the clinical condition of the patient is stable enough to be transported, and MRI scanned. The communication between the research team and the care team will be telephonic. Once the care team accepts and informs that the patient can be screened, the study personnel will check the compliance with inclusion/exclusion criteria listed, call the Patient's family or LAR to inform them about the study and will ask for verbal informed consent to screen the

patient. If the family agrees, the study personnel will schedule the screening/enrollment interview as soon as possible.

Prescreening Assessments Activities (days -90 to -1): The research team will only perform medical chart review of the patients that have an EEG requested.

- Assessing for an ordered clinical care EEG.
    - 2HELPS2B Assessment reviewed from the baseline EEG.
    - Stratification of Pre-Screening EEG Data (retrieved from medical record review).
        - EEG(+): had a **presence** of electrographic seizure, electroclinical seizure or ictal-interictal continuum.
        - EEG(-): was **negative** for electrographic seizure, electroclinical seizure or ictal-interictal continuum.
- Medical chart review: Presumed etiologies of disorder of consciousness, Epilepsy antecedent, other co-morbidities list, current spontaneous ventilation, height, weight, BMI, BSA, age, sex, pregnancy condition, supratentorial decompressive craniectomy, GCS score and current neurological responsiveness.
- Contacting care team to ask for clinical stability to MRI scan and authorization to contact the LAR.
    - Contacting the LAR to obtain verbal consent to administer the BIA.

Screening/enrollment interview (Day 0)

The screening will involve the in-person interview time period because the Barthel Index score is an additional test required to determine study eligibility. Thus, screening and enrollment will be performed on the same day, which is essential to reduce drop out during the screening period because the clinical state of these patients varies day by day. This strategy is also designed to reduce the anxiety of the families/LAR. The time frame to schedule the screening/enrollment interview after the phone call is flexible only to the extent that it must still meet the max 90 days enrollment deadline from MSABI. That means the available time to schedule the interview depends on the time since MSABI started, to meet the eligibility criteria. On the day of the telephonically scheduled interview with the LAR, the eligibility criteria by medical chart review will be double checked before the interview. If the patient is still eligible, the meeting will proceed. After presenting the study and its purpose, the study personnel will complete the Barthel Index (see appendix A) with the help of the LAR. If the score does not exclude the patient, the interviewer will explain potential risks and benefits and ask for consent for the study.

7.3.Enrollment

Once informed consent is obtained and the patient is enrolled, the coordinator will double-check previous history of porphyria, allergies, and hypersensitivity to the potential ASM listed in the study to provide a list of the treatment protocols that could be used for the patient if allocated to intervention. On the same day, the study coordinator will schedule the rs-fMRI for the following days and inform the research and the care teams of the scheduled date. This date should be within three days at maximum, and the intervention allocation must be done within six days from enrollment. Considering those dates, the minimum and maximum times from MSABI to the first rs-fMRI are 4, and 48 days correspondingly. The minimum and maximum times from MSABI to the intervention are 5 and 51 days, correspondingly. The family will be told that all the rs-fMRI results will be provided and explained after the follow-up research tests, and no further instructions are needed.

Screening/enrollment interview Activities (Day 0)

- BIS assessment for score (>80) through interview with potential LAR.
- Written Informed Consent Obtained from LAR.

- Consent must be obtained within 90 days from the participant's MSABI.
- Confirming baseline variables are collected through medical chart review.
  - Supratentorial decompressive craniectomy, current GCS score, presence of spontaneous ventilation.
- Verify with the LAR about: porphyria, co-morbidities, medical implants or contraindications for MRI, allergies, and hypersensitivity to the potential ASM.
- Provide a list of the treatment ASMs recommended for this participant that could be used if allocated to intervention.

- Notify Clinical Team about participant enrollment.
  - Verify with study team about which 2 combined ASMs could be administered in case of allocation to treatment.
    1. Phenobarbital 20 mg/kg loading dose
    2. Levetiracetam 60mg/kg loading dose
    3. Lacosamide 10 mg/kg loading dose
    4. Valproate 30 mg/kg loading dose
    5. Fosphenytion 20 mg/kg loading dose

7.4. Study Visits

This study is designed for in-hospital patients; no additional research team visits are planned. Clinical information after enrollment will be collected from medical charts (Glasgow coma score at the rs-fMRI#2 day), and the last data collection date at the outpatient clinic will be collected from medical records from the subjects that were discharged alive on ASM and scheduled to follow-up by one of the NSICU Post-Dischrage clinics. That visit is described under the next final visit section No. 7.5. For details about the in-hospital research activities visit Treatment Design section No. 6.

7.5. Final Visit

3 Months Post Day of Hospital Discharge

- Patients who are discharged will be seen in one of the NSICU Post-Dischrage clinics.
- The visits are scheduled at 3 months after hospital discharge.
- This visit is not scheduled by the research staff, and its information will only be obtained through medical chart review.
- The scales that are performed in patients that are seen in one of the NSICU Post-Dischrage clinics will evaluate functional, cognitive, and behavioral/psychiatric outcomes:
  - ASM toxicity: Liverpool adverse event profile test (LAEP) – If the patient is on ASM[36,37]
  - Cognitive outcome: Telephonic Montreal Cognitive Assessment (T-MoCA- 5mins protocol)[38]
  - Anxiety: PROMIS Emotional Distress—Anxiety— Short Form[39]
  - Depression: Neurological Disorders Depression Inventory for Epilepsy (NNDI-E)[40]
  - Quality of Life: QOLIE-10-P[41]

7.6. Phone Contacts

Not applicable.

7.7. Follow-Up Contact

The subjects will continue follow-up by their care team as appropriate, no research follow up subject visit is required beyond the 3-month from hospital discharge NSICU Post-Dischrage clinic visit listed in section 7.5.

7.8. Early Discontinuations

Data to be Collected The care team may adjust the treatment plan of all patients to ensure optimal medical management, including the study intervention. Patients who do not meet the treatment criteria (which requires treatment with two of the ASM regimens specified in the protocol for at least 72h from loading dose) or who are unable to undergo the rs-fMRI#2 after completing the minimum intervention time and within 72 hours of their last dose of the intervention protocol will be considered dropouts. For these patients, only the clinical data available at the time of enrollment and their initial rs-fMRI data will be collected for analysis of aim #2. However, this data cannot be used for other outcomes analysis. Nonetheless, we will still collect information about the reason for dropping out and any reported adverse events.

Subjects missing follow-up after rs-fMRI#2 and repeat EEG are performed will have all the study data already collected except for the data asked at one of the NSICU Post-Dischrage clinics for exploratory outcomes.

Criteria for Intervention Discontinuation

- Changes in the medical condition that contraindicate the use of at least two of the medications mentioned in the valid intervention list.
- Developing a medical condition that does not allow the rs-fMRI#2 scan.
- Presenting a grade 4 AE.
- Presenting a grade 2 to 3 AE without adequate measures to solve the event and prevent its study-related recurrence.

Requiring more aggressive ASM treatment because of seizures worsening or the need to change one ASM from the protocol list for another listed ASM is allowed.

7.9.Enrollees May Drop Out

Participants and/or their LARs may voluntarily withdraw from participation at any time, for any reason, with no penalty or loss of rights, or indicated treatment. The reasons for drop-out and missing data will be documented in the database. Drop-out from the study during the intervention phase will probably not imply patients leaving the hospital because of the intervention's short time frame and the target population's characteristic clinical condition. For those cases, we will schedule a personal interview between the research team and the LAR to solve doubts if the LAR accept by phone call. No efforts will be made to follow up with patients who drop out after the follow-up tests were taken because, after that time, the data collected is not relevant for the major outcomes of interest.

8. Statistical Analysis Plans

8.1. Strategies that Apply to all the Aims

All statistical procedures will be performed in SAS and R. Biostatistician Dr. Hongtu Zhu will oversee all data analyses.

(i) All data will be scored and rescored by separate staff members and checked for accuracy prior to double entry into our database. All datasets are backed up daily.

(ii) Prior to statistical modeling, we will perform descriptive analyses and data visualizations to examine the distributions of all measures. Appropriate transformations to obtain approximate normality will be performed; where necessary, additional nonparametric tests will confirm results.

(iii) Linear regression model and nonparametric tests (e.g., Wilcoxon rank sum test) will be the primary analytic tools for testing our *a priori* hypotheses. Model selection methods (e.g., Bayesian information criterion) and sensitivity analysis methods will be used to select models and assess various model assumptions. We will consider the use of appropriate covariates as detailed below in all aims.

(iv) We will record the reasons for drop-outs, missing / censored data values, and protocol departures in the database. We will appropriately handle drop-outs and missing data (e.g., missing responses and/or covariates) by using imputation or other estimation methods (e.g., missing completely at random), while considering anticipated causes. We will carry out sensitivity analysis to evaluate different missing mechanisms.

(v) We will use test statistics (e.g., likelihood ratio test) to test the hypotheses. To identify significant component terms in each of the models, we will examine the parameter estimates, 95% confidence intervals, and p-values of the component terms in an analysis of fixed effects for the final regression models. All statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CIs) and/or standard errors (SEs) to convey levels of precision / imprecision.

We will use graphical methods such as forest plots to visualize the analysis results. We will also include outcome-dependent exploratory analyses to generate new hypotheses.

8.2. Sample Description

We will use graphical figures (e.g., forest plots with tabulations, scatter plots, histograms, box-and-whisker plots, etc.) and descriptive statistical methods to describe the sample of individuals studied; they include graphical figures, counts, frequencies, sample means, sample standard deviations, percentiles, min, max, and standardized differences.

We will compare SzNET+/EEG+ with SzNET+/EEG- in terms of baseline/pre-treatment characteristics.

8.3. Aim-Specific Plans

Plans for Aim 1.

Aim 1 is to obtain preliminary data about the degree of improvement of seizure networks (SzNET) in moderate to severe acute brain injury (MSABI) patients after intervention's antiseizure medication (ASM).

Aim 1a

Measure the improvement of the SzNET total volume in MSABI patients after the intervention's ASM. The primary outcome of interest is the SzNET total volume median before and after the intervention's ASM in the target population.

H_0: there will be no difference in the SzNET total volume median in MSABI patients before and after the intervention's *ASM.*
H_1: SzNET total volume median in MSABI patients before ASM will be smaller than after the intervention's *ASM.*

Aim 1b

Measure the improvement of the SzNET power spectrum in MSABI patients after ASM. The outcome of interest is the SzNET power spectrum median before and after ASM in the target population.

H_0: there will be no difference in the SzNET power spectrum median in MSABI patients before and after the intervention's *ASM.*
H_1: SzNET power spectrum median in MSABI patients before ASM will be higher than after ASM.

We plan to recruit 11 patients with SzNET+EEG+ and 11 subjects with SzNET+EEG-. Therefore, 22 subjects with measurements before and after the intervention's ASM will be used in Aims 1a and 1b. We will fit linear regression models with dependent variables as follows. We calculate the changes of the SzNET total volume and the SzNET power spectrum before and after the intervention's ASM and use them as the primary dependent variables. Due to the small number of subjects, we only include an intercept to represent the mean difference before and after the intervention's ASM in the model, and we use the t-test statistic to test whether the intercept is equal to zero for Aims 1a and 1b. Moreover, we may consider demographic variables and pre-intervention EEG status (EEG+ or EEG-) if necessary.

Plans for Aim 2.

Estimate the frequency of EEG- and EEG+ patients presenting SzNET. The outcomes of interest are the proportions and differences of proportions of patients with SzNET among EEG- and EEG+ patients in this clinical setting.
For aim 2, we sequentially recruit SzNET+ subjects until the number of subjects in either SzNET+EEG+ or SzNET+EEG- first reaches 11 subjects. We will calculate the proportions of patients with SzNET among EEG- and EEG+ patients. and use the two-proportion Z-test to test their difference.

Plans for Aim 3.

Investigate association between post-intervention EEG improvement and SzNET response. The outcome of interest is the relative risk of EEG improvement in patients with more than 50% improvement of their SzNET by TVR and PSI.

H_0: there will be no difference in the EEG improvement between the patients with and without more than 50% improvement of their SzNET.
H_1: EEG improvement will be greater in the patients with more than 50% of SzNET improvement.

There are 22 subjects used in Aim 3. We will fit logistic regression model to characterize the association between the EEG improvement with *the patients with and without more than 50% improvement of* either PSI or TVR. We will use the Wald test and likelihood ratio test statistics to test the null and alternative hypotheses.

Plans for Aim 4.

Investigate association between the post-intervention typical resting state networks (RSN) connectivity improvement and the SzNET response. The outcome of interest is the relative risk of improvement of the typical RSN in the patients with more than 50% of improvement of their SzNET by TVR and PSI.

H_0: there will be no difference in the typical resting state networks connectivity improvement between the patient with and without more than 50% improvement of their SzNET.
H_1: Median typical resting state networks connectivity improvement will be greater in the patients with more than 50% of SzNET improvement.

There are 22 subjects used in Aim 4. We will fit logistic regression model to correlate the RSN improvement with *the patients with and without more than 50% improvement of* either PSI or TVR and use the Wald test and likelihood ratio statistics to test the null and alternative hypotheses.

Plans for Aim 5.

Describe psychosocial functional measure outcomes and ambulatory ASM toxicity at 3 months from discharge. The outcomes of interest will be the PROMIS Emotional Distress—Anxiety— Short Form, the Neurological Disorders Depression Inventory for Epilepsy (NNDI-E), the QOLIE-10-P, the Telephonic Montreal Cognitive Assessment, and the Liverpool adverse event profile test. All will be assessed at the 3 month follow-up visit to one of the NSICU Post-Dischrage clinics.

Plans for Aim 6.

Aim 6 is to assess the trial's design feasibility success in enrollment and retention by evaluating the enrollment rate and dropout rate among participants at the end of the trial.

Aim 6a

Measure the enrollment during all the months of study enrollment. The primary outcome of interest is the rate of monthly enrolled patients.

Aim 6b

Measure the participants dropout among participants during the study. The primary outcome of interest is the dropout rate among the total number of enrolled participants at the end of the study.

We will calculate the summary statistics of these measurements.

8.4. Planned Interim Analyses

No interim analyses will be performed.

9. Sample Size Rationale

There is no preliminary data for effect size estimation using the paradigm and patient population suggested in this study. In Aim 1, a paired t-test is used to test measurement differences before and after ASM. A effect size 0.806 can be detected for a 1-sided test at a power of 80% and a Type I error at 0.05 with the total of 11 subjects before and after ASM. In Aim 4, a transformed Z-test is used to test correlation between two variables. A correlation size 0.506 can be detected for a 1-sided test at a power of 80% and a Type I error at 0.05 with the total of 22 subjects.

10. Data Capture and Database Management

10.1. Software for Data Capture

The study personnel will enter the study data into a REDCap spreadsheet. REDCap is a HiPAA-compliant data capture system provided by the NC TraCS Institute at UNC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data will be entered directly from the medical chart, Rs-fMRI report, Core Disease CRF (appendix G) and one of the NSICU Post-Dischrage clinics forms (appendix H, I, J, K, L).

10.2. Responsibilities for Data Capture and Database Management

Data collection is the responsibility of the research staff at the site under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The study

coordinator or the coinvestigators that performs the consent interview will be responsible of interrogating the premorbid Barthel Index, initial filling up the Core Disease CRF and give it to the research staff to collect those data into the database.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data including adverse events (AEs), concomitant medications, and expected adverse reactions data) and research test data will be entered into **REDCap**, a HiPAA compliant data capture system provided by the **NC TraCS**. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.3. Study Records Retention

Study documents should be retained until at least 5 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the UNC Neurology Department and the Director of the UNC Clinical Resting State fMRI service.

11. Collection and Management of Tissue Specimens

11.1. Use in Current and Future Studies

If one of the combined doses administered is phenobarbital, on Day 2 the MD a blood sample will be collected for phenobarbital serum level (UNC Hospitals Test ID LAB30) to adjust the phenobarbital dose, aiming for a serum concentration of 40mcg/ml. The specimen collection will be ordered by the research team.

11.2. Sample Preparation

For thePhenobarbital serum levels measure 2 mL of blood are withdrawn by corresponding ICU nurse personnel from a central or arterial line using aseptic technic. If no adequate lines in place are available, the blood is acquired by phlebotomy performed by lab personnel. Immediately after withdrawal the blood is stored in a royal blue top tube or plain red top tube (no gel). After proper labeling with the research subjects MRN, it is transported at room temperature to the Core Laboratory for spin within 4 hours and further processing.

11.3. Record Keeping and Monitoring

The results will be informed and kept as regular tests done for clinical purposes. The results will not be stored by the research team, but will be used for safety purposes to provide a one time feedback to the care team in order to adjust dosing if deemed necessary.

11.4. Storage and Security

The sample will be stored, processed and discarded according to the usual standard procedures of UNC health Hem Onc Laboratory. It will not be kept for future research purposes.

12. Safety Monitoring and Management

12.1. Risk / Benefit Assessment

No psychological, social, legal or economic risks are anticipated with the study for the patients or the community.

Main Potential Risks (Based on frequency and severity):

Potential Risks: Physical risk of accidents during transportation to MRI scanner and scanning time.
This includes but is not limited to intravenous access displacements, falls, contusions, mechanical ventilation decoupling or displacement of medical devices.
Frequency: Uncommon to Rare.
Severity: Mild to severe, being rare the severe ones.
This risk is reduced by transport monitoring and care by a fellow physician, one respiratory therapist and two nurses. Enough clinical stability to transport to MRI scan by care team criteria is required.
Potential Benefits: For the individual participant the information acquired from the MRI scan can help guide treatment and can also provide useful information for neuro-prognostication. It also is the exam that defines the classification into intervention and no intervention groups.

Phenobarbital

Potential Risks: Physical risk of unknown hypersensitivity or unexpected reaction.
This includes non-dose dependent reactions like serious dermatologic reactions or drug reactions with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity, and dose dependent adverse effects presented while on the adequate range for age and weight like prolongation of QT. Electrocardiographic monitoring is standard of care for the ICU patients, which improves the safety of this drug use. Patients with porphyria will not be allocated to treatment with phenobarbital. Sedation or ventilatory depression by Phenobarbital are not relevant risks in this study because it would only be administered to patients that require ventilatory support. The risk of abuse and dependence on Phenobarbital is associated with use for prolonged periods of time so it also is not going to be considered.
Frequency of dermatologic reactions or hypersensitivity: Rare.
Severity: Mild to severe, being rare the severe ones.
Source: FDA labeling (appendix E)

Potential Benefits: As the rationale of this study explains, this medication could improve the control over epileptogenic activity, improving normal brain connectivity and clinical outcome, and in the context of the present study, will be administered to patients with abnormal resting state networks that are suspected of having an epileptogenic correlate. The available alternative options in the current clinical practice for MSABI patients with persistent consciousness compromise, risk of epileptogenic activity, and no electroencephalographic indication of increasing the ASM in their treatments are:

1. Wait for the clinical evolution assuming there is no additional benefit for stronger ASM and consciousness compromise is not related to the epileptogenic activity.
2. Increase the ASM regimen strength to test the hypothesis that epileptogenic activity might be involved in the consciousness compromise.

Levetiracetam

Potential Risks: Physical risk of unknown hyper sensibility or unexpected reaction.
This includes non-dose dependent reactions like serious dermatologic reactions or drug reactions with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity, and dose dependent adverse effects presented while on adequate range for age and weight like hematologic abnormalities.
Frequency of dermatologic reactions or hypersensitivity: Rare.
Severity: Mild to severe, being rare the severe ones.

Source: FDA labeling (appendix D)
Potential Benefits: As the rationale of this study explains, this medication could improve the control over epileptogenic activity, improving normal brain connectivity and clinical outcome, and in the context of the present study, will be administered to patients with abnormal resting state networks that are suspected of having an epileptogenic correlate. The available alternative options in the current clinical practice for MSABI patients with persistent consciousness compromise, risk of epileptogenic activity, and no electroencephalographic indication of increasing the ASM in their treatments are:

1. Wait for the clinical evolution assuming there is no additional benefit for stronger ASM and consciousness compromise is not related to the epileptogenic activity.
2. Increase the ASM regimen strength to test the hypothesis that epileptogenic activity might be involved in the consciousness compromise.

Lacosamide
Potential Risks: **Physical risk of unknown hyper sensibility or unexpected reaction.**
This includes non-dose dependent reactions like serious dermatologic reactions or drug reactions with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity, and dose dependent adverse effects presented while the on adequate range for age and weight like cardiac rhythm and conduction abnormalities.
Frequency of dermatologic reactions or hypersensitivity: Rare.
Severity: Mild to severe, being rare the severe ones.
Source: FDA labeling (appendix C)
Potential Benefits: As the rationale of this study explains, this medication could improve the control over epileptogenic activity, improving normal brain connectivity and clinical outcome, and in the context of the present study, will be administered to patients with abnormal resting state networks that are suspected of having an epileptogenic correlate. The available alternative options in the current clinical practice for MSABI patients with persistent consciousness compromise, risk of epileptogenic activity, and no electroencephalographic indication of increasing the ASM in their treatments are:

1. Wait for the clinical evolution assuming there is no additional benefit for stronger ASM and consciousness compromise is not related to the epileptogenic activity.
2. Increase the ASM regimen strength to test the hypothesis that epileptogenic activity might be involved in the consciousness compromise.

Valproate
Potential Risks: **Physical risk of unknown hyper sensibility or unexpected reaction.**
This includes non-dose dependent reactions like serious dermatologic reactions or drug reactions with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity, and dose dependent adverse effects presented while on the adequate range for age and weight like Hepatotoxicity and pancreatitis.
Frequency of dermatologic reactions or hypersensitivity: Rare.
Severity: Mild to severe, being rare the severe ones.
Source: FDA labeling (appendix F)
Potential Benefits: As the rationale of this study explains, this medication could improve the control over epileptogenic activity, improving normal brain connectivity and clinical outcome, and in the context of the present study, will be administered to patients with abnormal resting state networks that are suspected of having an epileptogenic correlate. The available alternative options in the current clinical practice for MSABI patients with persistent consciousness compromise, risk of epileptogenic activity, and no electroencephalographic indication of increasing the ASM in their treatments are:

1. Wait for the clinical evolution assuming there is no additional benefit for stronger ASM and consciousness compromise is not related to the epileptogenic activity.
2. Increase the ASM regimen strength to test the hypothesis that epileptogenic activity might be involved in the consciousness compromise.

Fosphenytoin

Potential Risks: Physical risk of unknown hyper sensibility or unexpected reaction.
This includes non-dose dependent reactions like serious dermatologic reactions or drug reactions with eosinophilia systemic symptoms (DRESS)/multiorgan hypersensitivity, and administration rate dependent adverse effects like cardiac arrythmias. Hematologic complications and local toxicity have been reported. It will not be administered in patients with porphyria.
Frequency of dermatologic reactions or hypersensitivity: Rare.
Severity: Mild to severe, being rare the severe ones.

Frequency of cardiac arrhythmia: rare at infusion rates of 150 mg phenytoin sodium equivalents (PE) per minute in adults and 2 mg PE/kg/min (or150 mg PE/min, whichever is slower) in pediatric patients.
Severity: Can be severe.
Source: FDA labeling (appendix B)
Potential Benefits: As the rationale of this study explains, this medication could improve the control over epileptogenic activity, improving normal brain connectivity and clinical outcome, and in the context of the present study, will be administered to patients with abnormal resting state networks that are suspected of having an epileptogenic correlate. The available alternative options in the current clinical practice for MSABI patients with persistent consciousness compromise, risk of epileptogenic activity, and no electroencephalographic indication of increasing the ASM in their treatments are:

1. Wait for the clinical evolution assuming there is no additional benefit for stronger ASM and consciousness compromise is not related to the epileptogenic activity.
2. Increase the ASM regimen strength to test the hypothesis that epileptogenic activity might be involved in the consciousness compromise.

The comprehensive mention of additional recognized AE related to the ASM listed on the protocol is included under section 12.3, “Grading the Severity of Adverse Events and Events of ‘Special Interest’”.

12.2. Assessment of Safety

The present study includes vulnerable populations unable to give consent which is addressed by LAR’s informed consenting process. It does not involve experimental drugs and employs clinical safety measures to prevent complications during the transport and scanning of the patients. Nonetheless the potential AE of diagnostic procedures and the ASM used for the intervention will be assessed by the following strategies:

- Eligibility criteria that imply checking for hypersensitivity or contraindications to the treatment protocol options that could be selected as the patient’s intervention. A selection of the non-contraindicated list of ASM for potential intervention use since the enrollment time reinforces this approach.
- Clinically indicated routine blood cells count, hepatic function, and renal function.
- Implementation of the clinical monitoring plan.
- Frequent direct communication between the care team and the research team.
- Severe adverse events (SAE) in enrolled subjects will pause the trial enrollment.
- The Independent Safety Monitor (ISM) will classify and report the AE. He will decide in which cases a meeting with the research or the care teams is needed for that task, and the assistants to the meeting. In case of mild to moderate adverse events found to be related, the research personnel will present a mitigating strategy. In the case of a SAE, the ISM will decide the conditions required to resume the trial or study end.
- Collection and analysis of safety variables to reassure and evaluate AE non-repetition strategies.

As criteria for individual research stopping, SAE will lead to retirement from the study as well as grade 2 to 3 AE without adequate measures to solve the event and prevent its study-related recurrence. Other events that

render the subject non-compliant with the enrollment criteria such brain death will retire the patient even if their occurrence was not triggered by the research activities.

12.3. Unanticipated Problems, Adverse Events, Serious Adverse Events

Unanticipated Problems: An unanticipated problem is any incident, experience or outcome that meets all three Office for Human Research Protections (OHRP) criteria (1) unexpected (in severity, specificity, frequency, or nature), (2) related or possibly related to the research, and (3) indicates that subjects or others are at a greater risk of physical, psychological, economic, legal, or social harm, as defined in UNC Office of human Research Ethics SOP.

Adverse Event (AE) Definitions: Any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the transportation and scanning time for the rs-fMRI#1 or rs-fMRI #2, or with the administration of one of the ASM listed as possible treatment protocol during the intervention phase, whether or not considered related to the subject's participation in the research.

Serious Adverse Events (SAE) Definition: Adverse event or suspected adverse reaction which is considered "serious" if, in the view of either the research team or the Neurology department, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include severe dermatological reactions or blood dyscrasias.

Grading the Severity of Adverse Events and Events of 'Special Interest': AE non classified as unrelated will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) scale v5.0 (appendix M) as follows:

Phenobarbital

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**

Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self-care ADL		

Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues.					
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL		
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal.					
Infusion site extravasation	Painless edema	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of the infusion into the surrounding tissue. Signs and symptoms may include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					

Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self-care ADL		
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site. **Navigational Note:** Prior to using this term consider specific edema areas: General disorders and administration site conditions: Edema face, Edema limbs, Edema trunk, or Edema neck; Nervous system disorders: Edema cerebral; Reproductive system and breast disorders: Genital edema; Respiratory, thoracic and mediastinal disorders: Laryngeal edema or Pulmonary edema; Skin and subcutaneous tissue disorders: Periorbital edema; Vascular disorders: Lymphedema					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL		
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony. **Navigational Note:** Prior to using this term consider using a specific body part pain term found throughout the CTCAE (over 40 different pain terms).					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Electrocardiogram QT corrected interval prolonged	Average QTc 450 - 480 ms	Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.					

Psychiatric disorders					
CTCAETerm	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**

Suicidal ideation	increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own lite.					
Suicide attempt			Suicide attempt or gesture without intent to die	Suicide attempt with intent to	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own lite					

Levetiracetam:

Psychiatric Disorders					
CTCAETem	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension					
Anxiety	Mild symptoms; interventio n not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by apprehension of danger and dread accompanied by rest lessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness.					
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Lite-threatening consequences, threats of harm to self or others; hospitalization indicated	-

Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable; medical or psychiatric intervention indicated	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid, extreme disorganization) ; hospitalization not indicated; new onset	Lite-threatening consequences , threats of harm to self or others; hospitalizatio n indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. lt may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					

Nervous system disorders					
CTCAE Tem	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrument al ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness.					
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention no indicated	Moderate symptoms; limiting instrument al ADL	Severe symptoms; limiting self-care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities					

General disorders

CTCAE Tem	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					

Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death

Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Neutrophil count decreased	<LLN - 1500/ mm3 ; <LLN - 1.5 X 10e9 /L	<1500 - 1000/ mm3; <1.5 - 1.0 X 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/ mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 X 10e9 /L	<3000 - 2000/ mm3; <3.0 - 2.0 X 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 X 10e9 /L	<1000/ mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					

Lacosamide

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Suicidal ideation	increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own lite.					
Suicide attempt			Suicide attempt or gesture without intent to die	Suicide attempt with intent to	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own lite					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention no indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated			
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Atrioventricular block complete		Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles.					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles.					
Ventricular tachycardia		Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His.					

Valproate

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hepatic failure			Asterixis; mild encephalopathy; drug induced liver injury (DILI); limiting self-care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death

Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time (INR.) Drug-induced liver injury (DILI) as defined by Hy's Law.

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pancreatitis		Enzyme elevation ; radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the pancreas with no documented pancreas infection.					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-

Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function.					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Platelet count decreased	<LLN - 75,000/ mm3; <LLN - 75.0 X 10e9 /L	<75,000 - 50,000/ mm3; <75.0 - 50.0 X 10e9 /L	<50,000 - 25,000/ mm3; <SO.O - 25.0 X 10e9 /L	<25,000/mm3; <25.0 x 10e9/L	
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					

General disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 ->82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

Fosphenitoin

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**

Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated			
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise	Death

Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes dueto rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His.					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hepatic failure			Asterixis; mild encephalopathy; drug induced liver injury (DILI); limiting self-care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time (INR.) Drug-induced liver injury (DILI) as defined by Hy's Law.					
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>l.5 - 3.0 x ULN if baseline was normal; >l.5 - 3.0 x baseline **if** baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Electrocardiogram QT corrected interval prolonged	Average QTc 450 - 480 ms	Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					

Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Eosinophilia	>ULN and >Baseline		Steroids initiated		
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood.					
Leukocytosis			>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					

Relatedness Definition: The research team, the clinical team and the independent safety monitor (ISM) will assess the likelihood of every SAE to be related to the research procedures and will classify the AE as:

- Unrelated
- Unlikely related
- Possibly related
- Probably related
- Definitely related

Non-SAE AE will be classify just by the ISM, and in both cases (SAE and non-SAE), to do so they will consider the following criteria:

- The AE has been previously reported for the suspected relatedness of ASM
- The temporal association between the ASM administration time and the AE is consistent with evidence-based literature.
- Other potential causes for the suspected AE were considered.

AE not classified as Unrelated will be considered to intervene with protective measures.

Expectedness Definition: The study personnel will evaluate if the related AE/SAE was expected. AEs different from transitory ventilatory decoupling are not expected during transport to MRI scans. The incident, experience, or outcome potentially related to one ASM listed is expected if reported in the FDA Online Label Repository in terms of nature, severity and frequency (see appendix B to F), and it is congruent with the subject's clinical condition.

AE and SAE Assessment, Follow-up Procedures: Multimodal monitoring and the daily paraclinical test indicated by the patient's clinical care will provide the means to detect the eventual AE. The research team and the ISM will actively search the medical charts for reported AE or concerning findings and establish direct communication with the care team to verify those findings to be considered an AE. Clinical conduct, including treatments required because an AE will be provided as needed by the care team, according to clinical management institutional guidelines. Meanwhile, the research team will verify the subjects' criteria to continue in the trial. For patients still able to continue in the study that presents an AE related to a specific intervention ASM, the care team and the research team will look to replace the related ASM with another from the protocol if that is safe for the patient and could let to complete the intervention criteria to perform the follow up tests. The clinical follow up required will be indicated by the care team and specific aims related follow up will be decided by the research team.

Reporting and Documentation Procedures: After the ISM analysis of each AE, the research team will report the event to the Neurology Department and the IRB by an NIH Clinical Research Toolbox Adverse event Form v2.0 (Appendix N). If the AE was classified as severity grade 4 or 5, or meets the UNC criteria for Promptly reportable information, it will be reported within seven days from the event; otherwise, the report will be stored at the clinical Resting State fMRI service and provided to the Neurology Department and the IRB as applicable. All those reports will be input in the corresponding safety variables and will be collected by the research team at the reporting time.
The Research team and the independent safety monitor will also look for any unanticipated problem (UP), which the study monitor will report it to the IRB and the Neurology Department with an NIH UP form (Appendix O), within seven days of the observed problem.

Participant Notification of New Information: Any new safety information known by the Research team will be provided to the actively enrolled subject or his LAR within five days and this communication will be reported in the electronic medical charts.
The anatomical MRI series will be reviewed and reported by the Radiology department of UNC health including whichever incidental finding. That anatomical image won't be reviewed in
detail by the research team, but will be used as part of the analysis process of the functional MRI sequences (BOLD). The functional MRI sequences (BOLD) won't give incidental findings, it would inform the state of resting state networks detected in the Subject. the presence of networks with features compatible with seizure networks will be disclosed to family and care team, because that finding will prompt the intervention arm allocation.

12.4. Safety Monitoring

The intervention phase of this study will occur while the participant is in the ICU, where constant medical care and observation are provided, so initial responses to adverse events will be in charge of the care team because they are the best suited for an on-time reaction. If emergent adjustments to the treatment plan are needed, those will be decided by the care team in direct communication with the research team when the time allows it. This communication will ensure compliance with the intervention criteria whenever possible, even if it implies switching an ASM for another one listed on the intervention protocol. Every adverse event related to a study subject being reported to the SAFE reporting system or identified by other non-specified means will be tracked by the study coordinator, who will inform the research team and the ISM, who will first decide if there is an identifiable unanticipated problem involved with the AE and then review the event to define its grade, its likelihood of being related to the study, the potential risk of recurrence, and how to prevent it. The ISM is free to schedule a meeting to complete those tasks, with the assistance of whom he determines. After the adverse event analysis, a study AE report classifying the event will be created (appendix N), and the AE that are not classified as

unrelated will be included in the reported safety variables. In case of severe adverse events, the meeting will also state the necessary conditions to resume the study or its definite early termination.

12.5. Study Suspension / Early Termination of the Study

The Study will be suspended and potentially prematurely terminated in the following situations:

- A severe adverse event occurs, and there is a concern for the risk of recurrence without an immediate and reliable preventive strategy.
- Happen three recurrent grade 2 to 3 AE of the same type implying noncompliance or inefficacy of the corrective measures.
- Notice of an *unanticipated problem* that implies an unfavorable risk benefit relationship for the intervention to the target population.
- The 25 percent of the maximum number of subjects to be enrolled have had the rs-fMRI#1 and no SzNET have been detected.
- A cumulative number of five enrolled patients allocated to the intervention do not reach to complete the intervention phase and get the research follow up tests.
- Any determination of serious or continuing noncompliance by the reviewing IRB.

If any of these situations is identified, it will prompt an asynchronous meeting or in person meeting, as determined by the ISM, for the research team to present an action plan to the Vice Chair of Research of the Department of Neurology. The Vice Chair will then assess the conditions for resuming the study, consider early termination if necessary, or convene a broader meeting as deemed appropriate. For those AE involving suspension and determination of being study-related, the resuming asynchronous or in person meeting will include the assistance of the ISM and whoever s/he determines as appropriate for the AE analysis.

13. Regulatory, Ethical, and Study Oversight Specifications

13.1. Informed Consent Process

The informed consent for the BIS screening test will be obtain verbally and the study's informed consent will be obtained using the informed consent form. Please see further details in section 13.1.2

13.1.1. Consent/Assent and Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Appendix P. Informed consent form.
- Appendix B FDA insert of Fosphenytion
- Appendix C FDA insert of Lacosamide
- Appendix D FDA insert of Levetiracetam
- Appendix E FDA insert of Phenobarbital
- Appendix F FDA insert of Valproate

13.1.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's or their LAR's agreeing to participate in the study and continues throughout the individual's study participation.
The first approach to the patient's LAR will be by telephone, presenting the researcher as non-care team personnel, part of a research team from the neurology department, and explaining the purpose of the call with a general idea of the study; then will ask for consent to schedule a personal interview to give further details of the study and the screening procedures. If the LAR accepts, an interview will be scheduled soon, in English or Spanish, according to the LAR preferences. The interview can be performed by one of the study investigators or by the research coordinator who will be trained to perform this activity.
At the interview, the screening process and the Barthel Index will be explained, if the LAR agree to continue the screening, the Barthel Index will be completed. For patients with a Barthel score of 75 or less the researcher will explain that the patient is not eligible for the study, in the case of a Barthel score of 80 or more the researcher will continue with the informed consent process to enroll the patient.

Consent forms will be Institutional Review Board (IRB)-approved and the participant's LAR will be asked to read and review the document. The investigator will explain the research study to the participant's LAR and answer any questions that may arise. A verbal explanation will be provided in terms suited to the LAR's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participant's LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant's LAR should have the opportunity to discuss the study with their family and think about it prior to agreeing to authorize the participation. The participant's LAR will sign the informed consent document prior to any procedures being done specifically for the study. Participant LAR must be informed that participation is voluntary and that subjects may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participant LAR for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to their LAR that the quality of their medical care will not be adversely affected if they decline to participate in this study. In case a research subject regains capacity to consent by neurological and mental medical exam, the research team will explain to the subject their current situation in the study and will explain all the study dispositions mentioned before to request for new consent. If the participant doesn't want to continue in the study, no further research studies will be performed, or new information collected, but the information obtained until that moment will be included in the study analyses.

13.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if defined stopping rules are met. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participant's LAR, the Neurology Department and the IRB.
If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and Neurology department and will provide the reason(s) for the termination or suspension. Active study participants or their LAR will be contacted and informed of changes to the study.

Examples of circumstances that may warrant termination or suspension of the study include:

- Criteria established in the Master protocol document (MPD) for early termination of the study have been satisfied
- Detection of an unexpected unacceptable level of risk to participants
- Futility due to insufficient adherence to protocol requirements.
- Unexpected inability to recruit participants.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and meets the requirements of the UNC Neurology department and the IRB.

13.3. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the UNC Clinical Resting State fMRI Service, the PICU, the NSICU, the SICU, the CICU, the CTICU, the MICU, and the Neurology Department. This confidentiality is extended to cover EEG recordings and rs-fMRI data in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of UNC.

All research activities will be conducted in as private a setting as possible.

The Neurology Department and representatives of the Institutional Review Board (IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at UNC Health information system site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and the Institutional policies requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the PI's UNC OneDrive account. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical site and by the UNC clinical resting state fMRI service research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in SOM Dept of Neurology Protected Research Database.

13.3.1. Certificate of Confidentiality

Not Apply.

13.4. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the PI's UNC OneDrive and The School of Medicine drive. After the study is completed, the de-identified, archived data will be transmitted to and stored at a private folder for the UNC Clinical resting State fMRI Service in the official School of Medicine drive, for use by other researchers including those outside of the study.
Permission to transmit data to the School of Medicine drive should be included in the informed consent. With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological data will be stored at the School of Medicine drive. The files at the School of Medicine drive will also be provided with a code-link that will allow linking the biological recordings (MRI imaging and EEG recordings) with the phenotypic data from each participant, maintaining the blinding of the identity of the participant. The blood samples collected for medication serum levels will not be stored, the results will be used just for treatment-dose adjustment purposes and not collected as research variables. This phenobarbital serum level information will be stored and managed in the same fashion as the patient's clinical information.

13.5. Key Roles and Study Governance

Principal Investigator,	**Principal Investigator**
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Research Coordinator	**Independent Safety Monitor (ISM)**
Yulissa Gonzalez	Afsaneh Pirzadeh MD
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- The two PIs and the UNC clinical Resting State fMRI Service manager constitute the Executive committee. It will provide project management for the entire project, including oversight of the execution and administrative functions.
- The Research Coordinator will assist the communication between care team, research team, ISM and the subject LAR.
- ISM will preside the AE meetings between the research team and the care team and will supervise the safety monitoring role of the research team.
- The experienced primary coordinators, backup coordinators, and administrative support to assist with regulatory compliance, budgets, and quality oversight will be provided by the Neurology Clinical Trials Unit. The research coordinator proposed in this trial will be trained by existing expert NCTU staff with expertise in onboarding new staff into key roles in clinical research.

13.6. Safety Oversight

Safety oversight will be under the direction of an ISM. Who will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The ISM will preside over the AE meetings and meet with the Executive Committee at the time of aim 2 analysis and six months from enrolling subjects to assess the safety and efficacy of the study. The ISM will provide its input to the Neurology Department.

13.7. Clinical Monitoring Plan (CMP)

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The monitoring will be provided by an ISM with experience in the use of ASM and not linked with the research team. This Monitoring will be centralized in UNC health at Chapel Hill and targeted to the patients with AE, providing a report for each case.

13.8. Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be discussed between the research team for clarification/resolution.
Following written Standard Operating Procedures (SOPs) from the Neurology Department, the monitor designee will verify that the clinical trial is conducted, and data are generated, collected, documented, and reported in compliance with the protocol, ICH GCP.
The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Neurology Department, and inspection by local and regulatory authorities.

13.9. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within ten days of identification of the protocol deviation, or within ten days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and reported to the Neurology department. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

13.10. Publication and Data Sharing Policy

Every attempt will be made to publish results in peer-reviewed journals. The PI will serve as first or senior author on all publications, with co-authors included according to journal guidelines. Data from this study may be requested from other researchers three years after the completion of the primary endpoint by contacting Dr. Varina Boerwinkle.

13.11. Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the University of North Carolina has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

14. Additional Considerations

Not Applicable

15. References

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