Cover page for VIGAB-STAT

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Clinical Study Protocol

EARLY VIGABATRIN AUGMENTING GABA-ERGIC PATHWAYS IN POST-ANOXIC STATUS EPILEPTICUS

VIGAB-STAT

PHASE IIA

A phase IIa feasibility trial of irreversible GABA-transaminase inhibition as adjunct treatment of status epilepticus after cardiac arrest

Version 14(11 May 2023)

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Contents

1. List of terms

ABG – arterial blood gas
AE — Adverse Event
AHA — American Heart Association
ASD – Antiseizure Drug
BSAS — Bedside Shivering Assessment Scale
CA — Cardiac Arrest
CI – Co-investigator
COSCA – Core Outcome Set for Cardiac Arrest
CPC — Cerebral Performance Category
CT — Computed Tomography
ED – Emergency Department
DNR — Do Not Resuscitate
DSMC — Data Safety Monitoring Committee
DWI – diffusion weighted imaging
eCRF — electronic Case Report Form
EEG — Electroencephalography
EMSE – Epidemiology-based Mortality Score in Status Epilepticus
EQ5D-5L — Euroqol health Survey 5 Dimensions 5 Level version
ESICM – European Society of Intensive Care Medicine
FOUR score — Full Outline of UnResponsiveness score
GABA — Gamma-AminoButyric Acid
GABA-t — Gamma-AminoButyric Acid transaminase
GFAP — glial fibrillary acidic protein
GOS – Glasgow Outcome Scale
GOS-E – Glasgow Outcome Scale-Extended
HRQOL – Health-related quality of life
ICU — Intensive Care Unit
IHCA — In-hospital cardiac arrest
ILCOR — International Liaison Committee on Resuscitation
IQCODE — Informant Questionnaire on Cognitive Decline in the Elderly
MoCA — Montreal Cognitive Assessment
mRS — modified Rankin Scale
MRI — Magnetic Resonance Imaging
NfL — Neurofilament Light chain
NG/OG – nasogastric or orogastric
NSE — Neuron Specific Enolase
OHCA — Out-of-hospital Cardiac Arrest
PASE — Post-Anoxic Status Epilepticus
PI – Primary Investigator
PD – Pharmacodynamics
PK — Pharmacokinetics
RASS — Richmond Agitation-Sedation Scale
REMS — Risk Evaluation and Mitigation Strategy
RN – Registered Nurse
ROSC — Return of Spontaneous Circulation
SAE — Serious Adverse Event
SF-36 – 36-Item Short Form Survey
SSEP — Somatosensory Evoked Potentials
TTM — Targeted Temperature Management
UCH-L1 — ubiquitin C-terminal hydrolase L1

UF – University of Florida
VFP – Visual Field Perimetry
VFQ-25 – Visual Function Questionnaire 25
VGB – Vigabatrin
WLST — Withdrawal of Life Supporting Therapies
WLST-N — Withdrawal of Life Supporting Therapies due to perceived poor neurologic prognosis

2. Trial overview

In 2015, the Institute of Medicine released a call to action for strategies to improve survival following cardiac arrest (**CA**)[1] given the lack of improvement in mortality rates and functional outcomes despite advances in resuscitation and the widespread use of targeted temperature management (**TTM**). By confirming the feasibility of using vigabatrin (**VGB**) as an early adjunct treatment for post-anoxic status epilepticus (**PASE**), while characterizing key pharmacokinetic and pharmacodynamics parameters in the post-CA setting, this trial pioneers the study of an innovative therapy for a deadly and frequent complication in the post-CA period.

The VIGAB-STAT study is a phase IIa trial exploring the feasibility of using VGB, a Gamma-AminoButyric Acid -transaminase (**GABAt**) inhibitor, as an early adjunct treatment for refractory seizures in CA survivors with PASE. This pilot trial aims to demonstrate the feasibility of enteral administration of a single load of VGB within targeted 48 hours of PASE onset in unconscious survivors of CA. The load of VGB is *in addition* to the load of a commonly used intravenous second-line therapy given at the discretion of the treating neurologist (e.g., phenytoin, valproic acid, phenobarbital, lacosamide, levetiracetam, etc). The key elements collected during phase IIa include: rates of screening, enrollment, and reasons for screen failure; ability to deliver VGB enterally within 48h of PASE onset; key pharmacokinetic parameters on absorption of VGB in this population and levels of other anti-seizure drugs; and ability to perform vision loss surveillance with taurine levels, Goldmann perimetry, and patient-oriented questionnaires.

3. Background and significance

Natural history of post-anoxic status epilepticus

Cardiac arrest claims millions of lives annually across the globe. Outcomes depend on resuscitation efforts and on the severity of global brain injury resulting from cessation of circulation (primary insult) and ongoing injury due to mismatches between cerebral energy supply and demand (secondary brain injury). Once return of spontaneous circulation (**ROSC**) occurs, the treatment relies on mitigating cerebral energetic demand. TTM is one of such treatments, but there is not a widely accepted practice across all post-CA patient population. This is because recent evidence questioned its role in affecting neurologic outcomes at 6 months compared to targeted normothermia [2] . Seizures, synchronized electrical phenomena produced by cortical neurons, are common after CA and lead to a marked increase in the cerebral metabolic activity and potential secondary injury. In fact, one in three unconscious CA survivors that undergo TTM experience PASE; TTM has not been shown to alter the frequency of post-CA seizures. Recent evidence suggests that early and aggressive treatment of PASE may lead to not only improved survival, but also functional independence [3-6].

Historically, PASE has been associated with nearly 100% mortality[4, 7-9]; however, the CA literature is confounded by bias due to variability in the provision of aggressive care when a low chance for functional recovery is perceived. As a result, this population has been traditionally excluded from observational studies and clinical trials of status epilepticus[10-15], and the management of these subjects varies widely[16, 17]. Further, non-standardized PASE treatment has failed to improve outcomes[18], leaving the Institute of Medicine's call yet unfulfilled. Despite increasing awareness of the potential positive impact of aggressive treatment of PASE with reports of neurologically intact survival [3-6], therapeutic interventions remain largely unexplored.

Subjects who develop status epilepticus while in the hospital tend to be refractory to first-line therapy (i.e., benzodiazepines) and are less likely to survive and return to a functional state[19]. Outcomes are indirectly proportional to status epilepticus duration[20-22] and latency to treatment[23]. Besides significant morbidity and mortality, status epilepticus and its treatment are associated with high hospital costs and prolonged length-of-stay[24, 25]. Moreover, while less than 50% of all status epilepticus patients are treated with anesthetics[26-28], PASE subjects more often receive them for practical reasons—often as sedatives to tolerate mechanical ventilation. PASE is also more likely to require aggressive treatment to reach seizure control[29]. Midazolam and propofol infusions are the forefront of treatment for refractory status epilepticus[11, 30-32] and are also the most commonly used sedatives during TTM. Recent pre-clinical studies have demonstrated potential benefits of a combined therapeutic strategy in status epilepticus aiming for synergistic mechanisms of action[33, 34], which may reduce duration and exposure to anesthetics and mitigate their associated morbidity[27, 35]. By identifying a novel indication of a drug with high potential for synergism and virtually devoid of safety concerns during short-term therapy, this study is the stepping-stone to filling an important knowledge gap in the care of CA survivors.

Rationale for a therapeutic trial exploring the GABA-ergic pathway

The GABA pathway is key in seizure initiation and termination[36]. During status epilepticus, there is marked alteration of GABA metabolism in this region promoting excitatory pathways; the rate of GABA synthesis decreases[37], GABA turnover time increases up to 3-fold[37], and cell surface GABA receptors migrate to the intracellular space[38-40].

Emerging evidence suggests that early and aggressive treatment of PASE may lead to good outcomes in selected cases[3-6, 41]; however, no standardized treatment has been proven beneficial in this population[18], and therapeutic algorithms are largely extrapolated from convulsive status epilepticus guidelines. First-line therapy acts by enhancing the $GABA_A$ receptor to increase its inhibitory tone. Vigabatrin, 4-amino-5-hexenoic acid or gamma-vinyl GABA, is a structural analog of GABA and irreversibly inhibits GABA-t—the enzyme responsible for GABA catabolism, thereby increasing brain levels of GABA. Vigabatrin may also stimulate GABA release [42]. The overall net effect is a significant elevation in GABA levels in nerve terminals, which facilitates GABA-mediated synaptic transmissions and leads to a marked and sustained antiseizure effect [43]. Its efficacy as adjunct therapy for intractable epilepsy is well-established in the literature[44-50]. In addition to its direct anti-seizure effects, VGB may potentiate the therapeutic effects of GABAergic anesthetics and antiseizure drugs (**ASDs**)[51, 52] that are commonly used in the post-CA period (e.g., propofol, midazolam, and valproate). Currently, VGB is an FDA-approved therapy for infantile spasms and refractory focal-onset seizures in adults. It is also being investigated as a neuroprotective therapy in traumatic brain injury[53, 54], though its role as an adjunct therapy in status epilepticus is unclear.

Rationale for chosen VGB regimen: A single VGB load is sufficient to achieve a prolonged GABA catabolism inhibition[55] and minimizes the risk of vision loss associated with chronic exposure. No toxicity has been reported with a single dose of VGB to date. The inhibition of central and peripheral GABA-t has been shown to outlast serum VGB elimination[55-57], demonstrating the irreversible nature of GABA catabolism inhibition[57, 58]. Vigabatrin has been tested up to 6,000mg daily doses in studies [59], including a study comparing placebo, 1,000/day, 3,000/day, and 6,000/day for a total of 12 weeks [60]. Additionally, 6,000/d dosing led to a similar therapeutic effect on seizure control than 3,000/d [60], but it was associated with increase sedation/drowsiness and led to higher proportion of patients discontinuing therapy. A dose ceiling effect has been set in initial studies of VGB, in which doses >60mg/kg failed to elevate cerebral GABA levels further[61], and prolonged elevations of cerebral GABA levels may reduce

GABA synthesis [61]. In an individual ~70 kg, 60mg/kg corresponds to 4,200mg. As absorption is expected to be lower in the post-cardiac arrest period (due to decreased gastrointestinal motility and gastric emptying), a single dose of 4,500mg was selected for patients with normal or mild renal impairment. Patients with moderate (CrCl 30-50mL/min) will receive 2,250mg (50% dose reduction), and patients with severe renal impairment (CrCl<30cc/min) will receive 1,125mg (75% dose reduction. Thus, to minimize toxicity risk, maximize synergistic potential with co-administration of GABA-ergic anesthetics and the therapeutic window, we selected a single loading dose of VGB.

4. Trial hypotheses and outcomes

Main objective and central hypothesis

Our overarching goal is to improve outcomes of successfully resuscitated individuals who experience refractory seizures following CA. Our central hypothesis is that early inhibition of GABA metabolism through VGB is possible in the post-CA period and may be an effective adjunct treatment for PASE.

Specific aims and hypotheses

Prove the feasibility of enteral administration of a VGB load within 48 hours of PASE onset in resuscitated CA subjects. We hypothesize that administering a single load of VGB within 48 hours of PASE onset is feasible. Later study phases will assess the potential therapeutic effects of this intervention.

Demonstrate the pharmacokinetics (PK) of VGB absorption in the post-CA period. We will follow VGB levels serially in the post-CA setting, in which there may be delayed absorption and impaired clearance. Delayed absorption is anticipated due to continuous enteral feeding, prevalent delayed gastric emptying enteric mobility, and decreased enteric blood flow in the setting of neuromuscular blockade and vasopressors. Impaired clearance may occur due to a high prevalence of renal insufficiency and older age. We hypothesize that VGB will be detectable in ≥80% and 100% of subjects by 3- and 12h, respectively. We expect that peak concentrations will be delayed from 1 to 3h post-VGB in older individuals (≥65-year-old) receiving continuous enteral feeding, and that delayed clearance (detectable VGB after 72h) will occur in CrCl ≤30cc/min [62-64].

Primary outcome

A. Primary feasibility outcome – enrollment and drug delivery
   We will primarily be looking at the ability to deliver VGB in PASE subjects; the target will be administering 4,500mg (or dose adjusted in moderate and severe impairment) of VGB enterally within **48 hours of PASE onset** in ≥ 80% of enrolled subjects. Given the lack of well-established alternative treatments in this deadly disease, we anticipate 60-75% enrollment of eligible subjects, and will therefore be tracking the ratio between eligible and enrolled subjects, consent rates, and reasons for decline in study participation.
B. Primary feasibility outcome – visual screening
   We will obtain serial taurine levels during ICU stay and Goldmann perimetry testing in the subjects are able to cooperate at 6 months follow up. Our goal is to achieve 90% completion rate for taurine levels, and have reliable visual field perimetry in ≥ 80% of survivors that regain consciousness following index hospitalization.
C. Primary pharmacologic outcome: PK – absorption
   By analyzing serial VGB levels including baseline, we will validate the drug assay and characterize drug absorption; the target will be achieving a detectable VGB level in the serum of ≥ 80% of

enrolled subjects by 3 hours post-load. We anticipate detectable levels in all subjects by 12 hours. We expect peak concentrations to be delayed by one to three hours in older individuals receiving continuous enteral tube feedings.

Secondary outcomes

A. Secondary feasibility outcome – PASE detection and ultra-early drug delivery
    a. We will track the proportion of subjects in whom PASE was present upon connection to EEG (onset misses) to explore alternatives to allow prompt EEG monitoring following ROSC.
    b. We will also track the proportion of enrolled subjects who received a VGB load within 12 and 24 hours of PASE onset to explore the possibility of ultra-early administration of VGB in subsequent phases, as the internalization of $GABA_A$ receptors (a key mechanism of treatment refractoriness) is time-dependent[65].
B. Secondary pharmacologic outcome: PK – elimination
    By analyzing serial VGB levels, we will characterize drug elimination. We anticipate undetectable VGB levels in all subjects by 7 days regardless of their renal function. Subjects with normal renal function will have undetectable VGB levels by 72 hours, and those with creatinine clearance less than 30 mL/min will have detectable VGB levels at 72 hours.

Exploratory outcomes

A. Exploratory efficacy outcomes
    a. Clinically oriented
        We will track the time from VGB load to resolution of PASE, time from VGB load to start of anesthetic wean, total duration of anesthetics for PASE treatment, the overall number of ASDs required for status epilepticus resolution, and the changes in neuron specific enolase (**NSE**), glial fibrillary acidic protein (**GFAP**), neurofilament light chains (**NfL**), tau and ubiquitin C-terminal hydrolase L1 (**UCH-L1**) over time as a potential indirect metric of neuroprotection since higher neuronal injury burden is associated with elevated NSE, GFAP and NfL levels.
    b. Physician-reported
        We will record Epidemiology-based Mortality Score in Status Epilepticus (**EMSE**) during index hospitalization to track disease severity. We will record the following outcomes at discharge, 6 months: modified Rankin Scale (**mRS**), Glasgow Outcome Scale- Extended (**GOS-E**), Glasglow- Pittsburgh Cerebral Performance Categories Scale original (**CPC**) and extended (**CPC-E**) in in person visits. In case subjects cannot attend in person visits, a structured questionnaire will be employed for telephone assessments (**t-mRS, t-CPC**). Cognitive function will be assessed by Montreal Cognitive Assessment (**MoCA**).
    c. Length-of-stay
        We will track total duration of anesthetic infusion for status epilepticus treatment, duration of mechanical ventilation, and ICU length-of-stay.
    d. Patient-reported
        We will evaluate self-perceived functional outcomes with the 36-Item Short-Form Health Survey (**SF-36**) according to the Core Outcome Set for Cardiac Arrest (**COSCA**) initiative recommendations on the use of outcome measures of health-related quality of life (**HRQOL**).

B. Exploratory safety outcomes
    a. Retinopathy
    Concentric visual defects have been reported with chronic use of VGB. As such, we will be detecting rates of retinopathy on vision loss screening via Goldmann perimetry upon regain of consciousness during index hospitalization (earliest time-point during which subject is able to cooperate with testing), ICU discharge and 6 months. In addition, long-term visual screening at 6 months will include the Visual Function Questionnaire 25 (**VFQ-25**). We do not expect to observe visual field restrictions with a single load of VGB as visual toxicity correlates with high doses and prolonged therapy. Concentric visual defects with chronic use of VGB may be related to a decrease in taurine levels. We will monitor taurine levels at baseline, 72 hours, and 7 days post-VGB administration. We anticipate that a single load of VGB would not lead to a statistically significant reduction in taurine levels.
    b. MRI brain
    Prolonged VGB therapy has also been associated with reversible MRI changes in the basal ganglia, thalamus, cerebellum, and brainstem. Unconscious CA survivors undergo brain MRI between 2- and 7-days post-CA for neuroprognostic purposes as a standard of care. We will note the proportion of subjects with MRI changes in the VGB cohort.
C. Exploratory pharmacologic outcomes
    a. Pharmacodynamics (**PD**) – ASD interactions.
    b. VGB may reduce or increase serum levels of ASDs. We will monitor daily levels of antiseizure medications that are co-administered with VGB for 3 days to characterize these potential drug-drug interactions and ensure optimal dosing.

Rationale for chosen outcomes

The phase IIa study is a feasibility study and is not powered to address efficacy or safety. We will collect these metrics and track percent of missing data and the time for completion to inform which clinical variables pertaining to efficacy and safety will become primary and secondary clinical outcomes in subsequent study phases.

The explicit purpose of this feasibility study is to deliver the drug within 48 hours of PASE onset and have measurable levels by 3-12 hours post-load in addition to completing visual screening. The reported bioavailability of VGB is 100%, with a wide volume of distribution, minimal binding to blood proteins and elimination mainly through renal clearance[42]. While plasma concentrations of VGB do not correlate with its effectiveness[42], they confirm successful absorption of this drug. Renal impairment is common after CA[66] and creatinine clearance influences VGB elimination[62]. Further, several other factors may affect VGB absorption in the post-CA period. Thus, we will follow serial VGB levels to characterize enteric absorption and clearance in this setting. Furthermore, given the potential for drug-drug interactions among ASDs, we will be monitoring other ASD levels. For example, up to a 20% reduction in total phenytoin plasma levels can be seen with co-administration of VGB[42, 67, 68], while up to a 10% increase in carbamazepine levels has been observed with co-administration of VGB[42].

Most landmark clinical trials with VGB did not include critically ill subjects. However, a recent trial evaluating the potential neuroprotective effects of VGB in severe traumatic brain injury demonstrated adequate absorption and elevated cerebral GABA levels as determined by microdialysis[53, 54]. Our study follows a design used in other studies, measuring serial VGB levels at baseline, 1, 3, and 12 hours following

VGB administration[53]; the addition of 0-, 0.5-, 1-, 2-, 3-, 6-, 12-, 24-, 48-, 72- and 168-hour (7 days) level measurements is aimed at accurately describing absorption, confirming clearance of the drug, and confirming the reported lack of correlation of drug levels with a sustained clinical effect. A pre-dose sample allows for confirmation that VGB is not already present in the study subjects and no interference in the quantification method.

Variation in anesthetic infusion weaning practices may confound the interpretation of successful wean from anesthetics. Further, anesthetics may be given to patients for other reasons than PASE treatment such as to maintain tolerability of mechanical ventilation and TTM. Thus, we chose to examine multiple secondary outcomes that could more accurately reflect the therapeutic effect of VGB and track the indication for maintaining anesthetic infusion rates daily. All the endpoints are objective and will be assessed by a blinded investigator to the timing of VGB administration.

5. Eligibility

Inclusion criteria

After Institutional Review Board approval, individuals (and their legally authorized representative) meeting the following inclusion criteria will be approached: 1) 18 – 80 years of age, 2) non-traumatic CA (regardless of non-perfusing rhythm, etiology, or location of arrest) in whom the decision to treat unequivocal electrographic SE (as defined by the American Clinical Neurophysiology Society[69]: having generalized spike/sharp-wave discharges ≥ 3Hz or any evolving pattern reaching > 4Hz, lasting ≥ 10 minutes, or comprising > 50% of any hour of recording) has been made. The inclusion criteria will be expanded to include presumed electroclinical status epilepticus defined in this study as ictal-interictal continuum patterns of at least 1Hz as long as patient is treated with an antiseizure medication per the decision of the clinical treatment team. The time of onset for PASE in this setting will be the time of the loading dose of antiseizure medication. 3) requiring anesthetic infusion for any reason, 4) have reliable arterial access for frequent blood sampling and 5) established enteral access within 48h of PASE onset. The patient's legal authorized representative (LAR) will be identified with the clinical, research, and social work teams. The legal authorized representative will be approached to provide consent for participation in the study, during the patient's acute phase of ICU care after cardiac arrest, while the patient is in coma, undergoing continuous seizure monitoring. In the event COVID related restrictions do not allow for the LAR to come to the floor, we will proceed with remote consenting procedures with IRB approved scripts. Should the patient regain consciousness at any time during the 6-month study duration, they will individually be approached to provide their consent for continued participation in the research protocol. Further details on consent process are provided in Section 9.

Exclusion criteria

Those with prior history of generalized epilepsy, history of gastrointestinal surgery within the last 21 days, and pregnant women will be excluded. In addition, those with PASE onset preceding initiation of EEG monitoring will be excluded.

Note on inclusion and exclusion criteria

Outcomes following successful resuscitation in CA are multifactorial and depend on both the severity of systemic (myocardial, renal, and liver dysfunction) complications and the neurologic post-CA syndrome. Post-anoxic status epilepticus may occur following any type of CA, regardless of the location of its occurrence (out-of-hospital versus in-hospital) or the type of non-perfusing rhythm. Thus, we will include

all non-traumatic types of CA in this study. As with other ASDs, VGB may exacerbate certain types of primary epilepsy. Thus, we elect to exclude individuals with a history of primary generalized epilepsy. Lastly, as there is no parenteral formulation of VGB, enteral access is a requirement for participation in this study.

Note on inclusion window

The window from SE onset to drug delivery of 48 hours is very short, particularly when consent from a legally authorized representative is pursued in the acute setting and enteral access for drug delivery is required. To expedite the process, we will approach the legally authorized representatives of potential participants for consent as soon as interictal epileptiform activity is identified on EEG as these subjects are at high risk for subsequent PASE[70-72].

Exit from the study

Any subject (or legally authorized representative) is free to withdraw consent from the trial at any time. Doing so will constitute exit from the study. The reason for withdrawal will be collected and reported, including specifics as to which aspects of the trial from which consent and participation are withdrawn (e.g., attending follow-up visits, completing diagnostic testing, and allowing for inclusion of their data (including survival data) in a database or publication. According to federal requirements for FDA-regulated clinical trials, all data collected up to the point of subject withdrawal must be maintained in the database and included in subsequent analyses, as appropriate. Legal authorized representative and/or subjects will be informed of this requirement.

Discontinuation of the study intervention by the treating physician due to any adverse events, for example, does not constitute subject withdrawal from the study, and therefore, the subject will not exit the trial.

6. Trial design

Phase IIa: This is a feasibility, single center, open-label pilot, with blinded outcome assessment, of early administration a single 4,500mg (or dose adjusted in moderate and severe impairment) VGB in 12 consecutive PASE subjects.

General critical care

General critical care will be standardized as much as possible for all subjects across various treatment sites. Management of fluid homeostasis, hemodynamics, respiration, metabolic disturbances, and seizures will be according to local protocols and standard of care.

Sedation

There will not be a specifically-defined protocol for sedation analgesia for the purposes of the study. Documentation will be required on the indication for changes in the level of sedation. The bedside nurse will notify the study coordinator when titration of sedatives is required and inform clinical reasoning.

For purposes of data analysis for clinical outcomes, thresholds will be established for anesthetic infusions, whereby dosing below the threshold will be considered comfort/sedative dosing only, while dosing above the threshold will be considered as anti-seizure treatment, regardless of the indication. The anesthetic

thresholds will be as follows: 1) midazolam ≥ 0.1 mg/kg/h, 2) propofol ≥ 50 mcg/kg/min, and 3) ketamine ≥ 1 mg/kg/hr.

Targeted temperature management

Post-CA practices are evolving with the emergence of highly impactful clinical trials and clinical practices of temperature modulation may vary. It is expected that a subset of patients will be treated with TTM, with target temperatures ranging from 32-37.5 degrees Celsius. Target temperature selection will be left at the discretion of treatment team. Details of TTM phase of care will be collected, whenever applicable.

Monitoring for and treatment of seizures

Continuous EEG monitoring will be connected as soon as possible after CA, with a targeted time from ROSC to EEG connection of 6-12 hours post-ROSC. For the phase IIa at the University of Florida, the order set for post-CA care includes a STAT order for EEG to be connected, which prompts the EEG technician to contact the bedside nurse to coordinate hookup.The clinical management of status epilepticus in the post-CA period has been standardized via a treatment algorithm at the University of Florida and UF Health Shands Hospital. Diversions from the algorithm will be at the discretion of the treating neurocritical physician and will be documented in study records.

Monitoring for markers of secondary brain injury (chemical biomarkers)

We will compare changes on NSE over time between VGB-treated and non-VGB-treated PASE subjects as a potential indirect metric of neuroprotection as higher neuronal injury burden is associated with elevated NSE [73-75], GFAP and NfL[76]. Biomarkers will be measured serially at five timepoints including at 0h, 24h, 48h, 72h, and 4d (96h) post vigabatrin administration.

Shivering

Shivering will be assessed according to the Bedside Shivering Assessment Scale (**BSAS**). Goals of treatment are to maintain BSAS score 0-1, which will be done for all subjects and tiered prevention and therapeutic approach will be implemented according to institutional practices.

Screening

Screening will be done according to the inclusion and exclusion criteria and will be performed in multiple clinical areas, including the Emergency Department and ICU. The PI and co-investigators will be responsible for screening the EEG of eligible subjects for PASE development four times daily.

We will maintain a screening log to keep track of all eligible subjects, which will inform future decisions on inclusion/exclusion criteria in the subsequent study phases.

Blinding

The phase IIa feasibility study is open label. However, EEG recordings and Visual Field Perimetry will be centrally analyzed at the EEG and Visual Screening cores by an assessor that is blinded to the timing of VGB administration and drug levels. De-identified EEG recordings will be exported to Yale University for central analyses by Dr. Hirsch, and de-identified Visual Field Perimetry studies will be exported to Dr. Sergott at Tomas Jefferson University for central analyses in a blinded fashion. Clinical outcomes will be obtained by trained study personnel blinded to the timing of VGB administration and drug levels.

Intervention period

Drug administration

University of Florida (**UF**) Health Shands Hospital is enrolled in the Vigabatrin Risk Evaluation and Mitigation Strategy (**REMS**) program. The Vigabatrin drug supply for this protocol will be purchased, stored, and dispensed through the Investigational Drug Services Pharmacy satellite of the UF Health Shands Hospital Pharmacy Department. The study drug will be segregated from commercial supply Vigabatrin. Investigational supply would be dispensed upon enrollment, consent, and receipt of a valid order for investigational supply Vigabatrin by a protocol authorized prescriber. Prior to dispensing, the protocol-trained, REMS-trained pharmacist would verify the authorized prescriber, patient REMS enrollment, document the REMS ID numbers and obtain authorization to dispense through the REMS program.

Subjects will receive a **one-time loading dose of 4,500 mg of VGB** (or dose adjusted in moderate and severe impairment) in powder for oral solution formulation (9 packets of 500mg each, each mixed with 10 ml of water at room temperature, for a total of 90 ml of water and 4,500mg VGB dosing) will be administered via enteric tube (naso/orogastric or post-pyloric) within **48 hours of status epilepticus onset**. For subjects requiring a dose adjustment for renal impairment, the total volume administered will be dictated by dose of Vigabatrin (10mL of water for each 500mg packet).. If subjects are receiving the study drug through an NG/OG tube that is ordered to be connected to suction, the tube will remain clamped for a minimum of 30 minutes. Vigabatrin will not be co-administered with other enteral drugs, and no drugs will be given +/- 15 minutes of Vigabatrin administration (when possible per standard of care). Subjects will be considered screen failure if VGB is not administered within exact 48 hours from electrographic status epilepticus onset. This dose is in conjunction with a loading dose of ASD according to local practices and standard of care. This will be done within 48h of PASE onset in successfully resuscitated CA subjects.

Drug absorption

VGB level will be monitored serially at baseline (prior to load), 0.5h (+/- 5 minutes), 1h (+/- 5 minutes), 2h (+/- 15 minutes), 3h (+/- 15 minutes), 6h (+/- 15 minutes), 12h (+/- 15 minutes), 24h (+/- 30 minutes), 48h (+/- 30 minutes), 72h (+/- 30 minutes), and 7d (168h) (+/- 30 minutes) post-VGB administration along with daily levels of concurrent ASD. All PK samples will be collected from an arterial line. If sufficient arterial access is not available at the scheduled time, peripheral venipuncture will be the preferred second method of blood collection, and will be noted in source documentation. The study team will provide support to clinical nursing staff in order to ensure prioritization and timeliness of study-specific activities.

After the intervention period

Screening for visual adverse events

The main adverse effect associated with VGB is visual loss from retinopathy [77, 78], which may lead to concentric visual field defects that may be related to taurine deficiency. Therefore, vision loss surveillance comprised of serial taurine levels and Goldmann perimetry (to assess visual changes/visual loss should the patient regain of consciousness), during their 6 month follow-up visit; Goldmann perimetry is a validated method to monitor for and quantify potential effects of VGB treatment [79-83]. In addition, a VFQ-25 will be administered at 6-month follow up visit.

Other anticipated adverse events

The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection. As arterial and central line catheters are used for several days in the post-cardiac arrest period, these risks associated with the blood draws are less likely to occur when blood sampling is not via puncture.

The adverse events commonly seen with continued use of VGB (such as fatigue, somnolence, dizziness and imbalance, abnormal eye movement, tremor, memory impairment, weight gain, joint pain, and confusion) are less expected to be evident in this patient population, as coma precludes the assessment of pain, fatigue, and cognitive symptoms.

Prognostication

Clinical examination

Per standard of care, a daily sedated neurological exam will be completed on each subject. Attention will be paid to presence of myoclonus post-CA and its semiology, the presence of any clinical correlate to electrographic PASE, and the coma exam. We will also collect pupillometry measurements during daily neurological exams and at 1h post VGB load. We subscribe to the AHA and ESICM guidelines, which highly encourage the use of a multimodal approach to neuroprognostication. Current guidelines recommend a minimum of 72 hours post-complete rewarming before neuroprognostication to give every effort to avoid premature WLST in subjects with a chance of neurological recovery.

EEG

A minimum monitoring of 72hours post-ROSC is standard of care at University of Florida. The presence of epileptiform discharges, continuity, and reactivity of background to a standardized protocol of escalating external stimulation will be noted.

Brain CT

In accordance with local practices, a noncontrast CT of head is strongly recommended in cases of unclear CA etiology. The presence of early hypoxic-ischemic brain injury such as gray-white differentiation and diffuse cerebral edema will be noted. In subjects that do not regain consciousness within 48 hours of ROSC, a repeat noncontrast CT is recommended for prognostication.

Brain MRI

MRI brain without gadolinium will be obtained in post-CA unconscious subjects within 2-7 days of ROSC, if deemed safe according to the treatment team according to local prognostication practices. The presence of hypoxic-ischemic brain injury, and the pattern of DWI restriction will be noted.

NSE

Serial NSE (daily for 5 days) is obtained according to local prognostication practices. The presence of hemolysis and the type of assay used, as well as titers will be recorded.

SSEP

Somatosensory evoked potentials are a reliable prognosticator after 48hours of ROSC. The presence or absence of N20 peaks will be noted.

VIGAB-STAT criteria for a likely poor neurologic outcome

Death

The time and mode of death (related to WLST or care limitation, recurrent and refractory CA, brain death) will be noted. Brain death will be determined by institutional protocol and if organ support is maintained for reasons other than the purpose of the study, study data will continue to be obtained with patient LAR approval.

WLST

Goals of care and decision making related to end of life will be led by treatment teams. EEG monitoring will continue as long as the subject remains in PASE until the decision of withdrawal of life sustaining therapies and transition to comfort measures only is made.

Recurrent cardiac arrest

With recurrent episodes of CA, subjects will remain eligible following ROSC as long as the decision to maintain aggressive care is in place.

Follow up

Formal follow-up appointments will be conducted at 6 months (+/- 1 month) post-CA, whether the subject remains hospitalized or discharged. A voucher of $25.00 will be provided upon discharge to assist with transportation for the 6 months visit. Follow-up appointments will be conducted by blinded assessors and focusing on cognitive function, quality-of-life, and recurrence of seizures. The assessor may be any qualified provider including physician, research nurse, or extended provider. The assessment will consist of a structured telephone interview for those that are unable to participate in in person visits. Epilepsy assessment will consist of a brief questionnaire asking about recurrent seizures and number of ASD required for maintenance therapy.

7. Co-enrollment

MOCHA and SPARE

When meeting inclusion criteria, participating centers also involved in the MOCHA and/or SPARE trials will obtain consent and co-enrollment in the appropriate trial(s). The MOCHA trial is an observational trial, and co-enrollment with other studies (registries or interventional trials such as VIGAB-STAT) is permitted as long as the other study protocols do not call for premature neuroprognostic assessments earlier than 72 hours post-CA. Therefore, each subject's co-enrollment eligibility will be reviewed on a case-by-case basis. If enrolling sites are in agreement, and the studies under consideration at a given site are approved by the Steering Committee, the subject may be co-enrolled in MOCHA, SPARE, or other studies.

8. Data Collection

Test/Lab	Baseline	D0	D1	D2	PASE	VGB Administered (0h)	0.5h	1h	2h	3h	6h	12h	24h	48h	72h	96h	120h	168h	D14/ICU Discharge	Hospital Discharge	D180
Review of Eligibility: Inclusion/Exclusion Criteria	X	X	X	X																	
Demographics	X																				
Informed Consent		X	X	X																	
Medical History		X																			
Vitals		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
Cardiac-specific Treatments and Assessments		X																			
Neurological Assessments		X	X	X	X	X							X	X	X	X	X	X	X	X	X
Pupillometry		X	X	X	X	X		X					X	X	X	X	X	X	X		
FOUR		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	
Medications		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X
mRS																				X	X
GOS-E																				X	X
CPC-E																				X	X

MoCA																				X
EMSE																			X	
VGB level						X[c]	X[e]	X[e]	X[f]	X[f]	X[f]	X[f]	X[g]	X[g]	X[g]			X[g]			
Standard Anti-seizure drug level						X[c]		X		X		X	X		X			X			
Routine complete blood cell count, complete metabolic panel, ABG, lactic acid	x	x	x	x	x						x		x	x	x	x	x	x			
Biomarkers: NSE, GFAP, NfL, UCH-L1, tau						X							X	X	X	X					
Taurine level						X[c]									X			X			
cEEG		X	X	X																	
MRI Window															X	X	X				
Goldmann perimetry																					X
VFQ-25																					X
Clinical Events		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	
Discharge Summary																				X	

a Time in days (D) refers to time from CA, while time in hours (h) refers to time from VGB load, unless otherwise specified.

c Baseline testing will be done prior to administration of VGB load.

d Baseline testing will be done as soon as the patient is able to cooperate.

e Acceptable window for collection is +/- 5 minutes.

f Acceptable window for collection is +/- 15 minutes.

g Acceptable window for collection is +/- 30 minutes.

Baseline data

Subject characteristics

- Inclusion/exclusion criteria
- National identification number
- Demographics

Pre-hospital data

- Drugs administered

Background data

- Medical history
- Home medications
- Factors predisposing to seizure (e.g., prior traumatic brain injury or other structural injury, history of epilepsy, congenital malformations)
- Routine blood work (standard of care): complete blood count, complete metabolic panel, ABG, Lactic Acid

Data on hospital admission

- FOUR-score
- Neurological assessments
- Signs of PASE prior to EEG monitoring

Data on ICU phase

Data prior to VGB load

- VGB level
- ASD level
- Taurine level
- Brain injury biomarkers panel: NSE, tau, GFAP, UCH-L1, NfL
- Pupillometry measurements

Data during the intervention

- FOUR-score
- Pupillometry (1h post VGB load)
- Levels and labs as in chart, including all daily blood work obtained as standard of care
- Brain injury biomarkers panel: NSE, tau, GFAP, UCH-L1, NfL for 5 days following VGB

Daily during the ICU stay

- FOUR-score
- Neurological assessments and pupillometry
- Serious adverse events (SAEs)
- If active intensive care is withdrawn, specify reason
- Levels and labs as in chart, including all daily blood work obtained as standard of care
- Code status, changes in code status, and level of medical intervention

Status epilepticus data

- Time from VGB load to resolution of PASE
- Time from VGB load to start of anesthetic wean
- Total duration of anesthetic infusion for SE treatment
- Overall number of anti-seizure drugs required for PASE resolution
- EMSE

At ICU discharge

- FOUR-score
- Time when obeying verbal commands (awake – FOUR-score M4)
- Duration of mechanical ventilation
- ICU length of stay
- CPC, mRS, GOS-E

At hospital discharge

- FOUR-score
- Discharge status (e.g., good, fair, stable, poor, critical, dead)
- CPC, mRS, GOS-E, first portion of CPC-E
- Discharge destination

180 days after intervention

- Survival status
- CPC, mRS, GOS-E, second portion of CPC-E
- MoCA
- Goldmann perimetry
- VFQ-25
- SF-36

9. Ethics and informed consent

Informed consent from a legal authorized representative, including counseling and enrollment required in accordance with Risk Evaluation and Mitigation Strategies (REMS) program by a certified REMS physician, will be obtained for all patients prior to VGB administration. The consent form must also be signed by the investigator seeking the consent. In the event of COVID related restrictions preventing the LAR from coming to the floor, the research staff will email the informed consent to the LAR and schedule a time for the PI and the LAR to discuss the trial. This will be documented according to Good Clinical Practice standards. The study will be explained described to the legal authorized representative in an appropriately considerate manner by the principal investigator or certified REMS physician co-investigator, and the legal authorized representative will have opportunity to ask additional clarifying questions.

The social worker assigned to the case (either in the ED or the ICU) will assist with the timely and accurate identification of legal authorized representative (LAR). The LAR will consent on behalf of the subject per regulatory requirements, until such time that the subject is able to consent for themselves. This is deemed to be consistent with the Declaration of Helsinki article 30 available from the World Medical Association.

Subjects regaining consciousness will be assessed for capacity by the treating neurologist, and if deemed to have capacity to participate in the informed consent process, will be asked for written consent as soon as they are able to make an informed decision. Assessment for capacity will be completed on an as-needed basis. The consenter will be provided with written and oral information on this trial to make an informed decision about participation in the trial. LARs will be counseled that decisions on research participation should be made in accordance with the subject's values and wishes. If these are unknown, the LAR will be counseled to make such decisions in the best interest of the subject. Potential subjects and their LARs will only be approached after the attending physician responsible for care of the patient has discussed the potential subject's prognosis (including the possibility of terminal illness or disability) with the potential subject and LAR. The investigator will coordinate directly with the attending physician to ensure this discussion has occurred prior to informed consent. The consent form must be signed by the participant or legally acceptable surrogate and by the investigator seeking the consent.

10. Data management

Data handling and record keeping

Individual subject data will be handled according to HIPAA and individual institutional policy. All subject data will be made anonymous when translated to study database. Raw EEG recordings will be de-identified, assigned a study ID, and exported in EDF format to Yale University via secure cloud system. Visual Field Perimetry will be de-identified, assigned a study ID, and exported to Tomas Jefferson University for central analyses via secure cloud system.

Quality control and quality assurance

This trial will be monitored independent of the institution by a hired service. The frequency of on-site monitoring will depend on compliance with the protocol, number of enrolled subjects and data handling. At a minimum, there will be a pre-study visit, one during the study, and one post-study. All participating sites will abide by the same quality control protocol, CRF, inclusion/exclusion criteria, registration instructions, randomization protocol, and specific medical treatment protocols.

11. Adverse events

Definitions

Defining adverse events and distinguishing between these and sentinel events will be the sole responsibility of the primary and each local investigator. Documentation and reporting of events will depend on institutional policy and the local investigator.

An adverse event (**AE**) is any untoward medical occurrence in a clinical trial subject. These are expected in all subjects with ROSC from CA, and therefore, AEs that may be related to study intervention will be reported.

Safety monitoring plan

The principal investigator will monitor the patient safety data for each AE and serious AE within 24 hours of occurrence. Several serious adverse events are expected to occur given the severity of the condition being studied. Each adverse event will be adjudicated to determine if it is possibly related to the study drug or unrelated. If the principal investigator feels there is possible harm to subject safety or the possibility of, any harm due to something new that was learned during the study, she will activate the multi-disciplinary Data Safety Monitoring Committee for this trial. The Data Safety Monitoring Committee is comprised of a Neuro-Ophthalmologist (Dr Bryce Buchowicz), 2 Neuro-intensivist (Dr. Katharina Busl and Dr. Michael Pizzi), 1 Medical Intensivist (TBD). The committee will meet to discuss and review any referred event.

Additionally, this study will have a designated Data Safety Monitoring Board comprised of 5 members without ties to the current study or any conflicts of interest: 1 Emergency Medicine and Critical Care specialist (Dr. Casey Carr), 1 general neurologist with expertise in clinical trials (Dr. -Matthew Burns), 2 epileptologists (Dr. Giridhar Kalamangalam and Dr. Maria Bruzzone), 1 cardiologist (Dr. Alexander Parker), and 1 Pulmonary Critical Care specialist (Dr. Ali Khawaja). The DSMB will be charged with the duty of meeting every 6 months to discuss all the adverse events for the study, and generate a written report which will be submitted to the IRB. The DSMB will be informed of all serious adverse events and all mild adverse events which are potentially study-related in the opinion of the investigator. The PI will designate each adverse event as mild or severe; determine relatedness to intervention; and indicate anticipated or unanticipated. The DSMB may employ a stopping rule for greater than 1 drug related death.

Reporting of serious adverse events

A serious adverse event (**SAE**) is defined as any event that:

- Results in death
- Is life-threatening
- Requires hospitalization or increased length of stay
- Results in persistent or significant disability or incapacity

12. Statistical plan and data analyses

Phase IIa sample size

12 subjects from the University of Florida

Analysis methods

This feasibility pilot is not intended to detect therapeutic effects. Thus, we have omitted power calculations.

Primary outcome

Descriptive statistics with rates and proportions will be obtained regarding feasibility outcomes. Regarding the PK outcome, we will use the noncompartmental method for pharmacokinetic analyses. The key pharmacokinetic parameters, maximum concentration in plasma (C_{max}) and the time to reach

maximum concentration (T_{max}) will be determined directly from the plasma concentration-time profile of each participant. The area under the VGB concentration-time curve in plasma from zero to the time of the last quantifiable concentration ($AUC_{0\text{-}tlqc}$) will be calculated using the linear trapezoidal methods, and the AUC will be extrapolated to infinity for the evaluation of $AUC_{0\text{-}inf}$.

Secondary outcome

For exploratory aim 1, we will calculate the rate of retinopathy and the proportion of subjects with MRI changes. For exploratory aim 2, standard summary statistics will be provided for the post-VGB time to resolution of PASE, post-VGB time to start of anesthetic wean, overall number of anti-seizure drugs required for PASE resolution, total duration of anesthetic infusion for PASE treatment, duration of mechanical ventilation, intensive care unit length-of-stay, and cerebral performance category scale at hospital discharge and at 6 months.

Missing data

Missing data will be reported.

Subgroup analysis

Subgroups that will be analyzed during subsequent phases of the trial include:

- GFR
- Need for and mode of renal replacement therapy
- Type of feedings
- Elderly vs non-elderly
- Neuromuscular blockade
- Vasopressor use

13. Publication of data

The trial will be analyzed by an independent statistician, and the results interpreted by the steering group. All individual data will remain confidential. The final manuscript will be submitted to a peer-reviewed international journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement. The author list will include the steering group members, national investigators, and additional names in alphabetical order.

14. Insurance

15. Funding

American Heart Association Innovative Project Award 20IPA35380013

16. Timeline

Project Start Date: April 10th, 2021

17. Trial participants

Steering Committee:

Carolina Maciel, MD	PI, Neurocritical Care, University of Florida
Lawrence J. Hirsch, MD	EEG Core, Chief of Epilepsy, Yale University
Charles Peloquin, PharmD	PK Core, University of Florida
Robert Sergott, MD	VS Core, Chief of Neuro-Ophthalmology, Wills Eye Hospital
David M. Greer MD, MA	CI, Neurology, Boston University
Alejandro Rabinstein, MD	CI, Neurology, Mayo Clinic
Ramani Balu, MD, PhD	CI, Neurology, University of Pennsylvania
Eugene Ramsay, MD	CI, Director of Ochsner Comprehensive Epilepsy Center
Monica Dhakar, MD	CI, Neurology, Emory University
Kent A. Owusu, PharmD	CI, Yale-New Haven Health
Stephan Eisenschenk, MD	CI, University of Florida

Investigators responsibilities

18. Appendices

FOUR score

A The FOUR Score

Eye response	
Eyelids open and tracking, or blinking on command	4
Eyelids open but not tracking	3
Eyelids closed but open to loud voice	2
Eyelids closed but open to pain	1
Eyelids closed with pain	0
Motor response	
Makes sign (thumbs-up, fist, other)	4
Localizing to pain	3
Flexion response to pain	2

Extension response to pain	1
No response to pain	0
Generalized myoclonic status	0

Brainstem response

Pupil reflexes present, corneal reflexes present, and cough present	4
One pupil wide and fixed, corneal reflexes present, and cough present	3
Pupil reflexes absent, corneal reflexes present	2
Pupil reflexes present, corneal reflexes absent	2
Pupil reflexes absent, corneal reflexes absent, cough present	1
Pupil reflexes absent, corneal reflexes absent, cough absent	0

Breathing

Not intubated with regular breathing	4
Not intubated with Cheyne-Stokes type of breathing	3
Not intubated with irregular breathing	2
Not intubated with apnea	0
Intubated with breathing above ventilator rate	1
Intubated with breathing at ventilator rate	0

mRS

B	Modified Rankin Scale
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities.
2	Slight disability; unable to perform all pervious activities but able to look after own affairs without assistance.
3	Moderate disability; requires some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent, and requires constant nursing care and attention.

6 Dead

CPC

C Cerebral Performance Category (CPC) score scale

CPC1 Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.

CPC2 Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.

CPC3 Severe cerebral disability: conscious, dependent on other for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.

CPC4 Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.

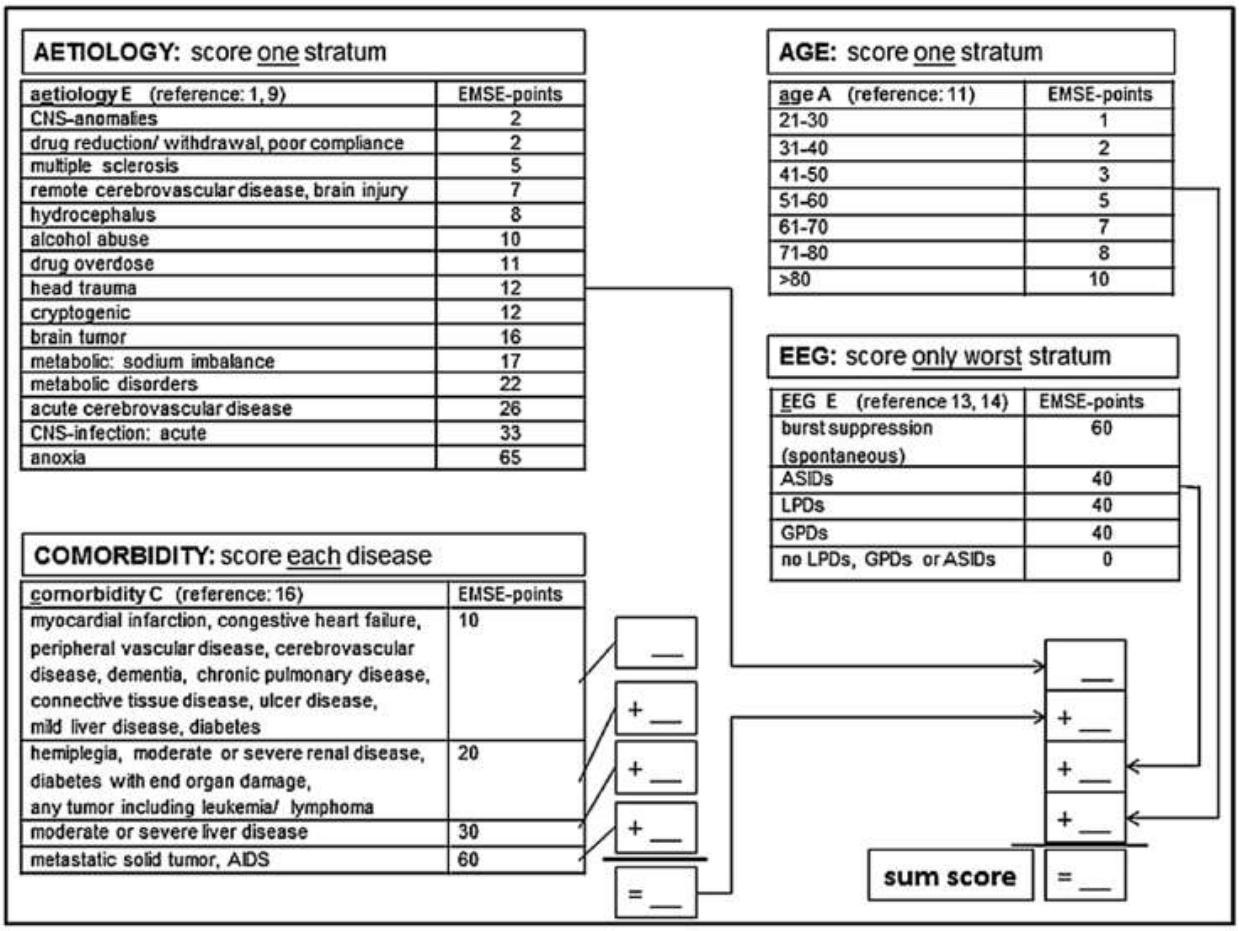
CPC5 Brain death: apnea, areflexia, EEG silence, etc.

Glasgow Outcome Scale – Extended

1	Death
2	vegetative state
3	lower severe disability
4	upper severe disability
5	lower moderate disability
6	upper moderate disability
7	lower good recovery
8	upper good recovery

Epidemiology based Mortality score in Status Epilepticus (EMSE)

D EMSE Scoring



AETIOLOGY: score one stratum

aetiology E (reference: 1, 9)	EMSE-points
CNS-anomalies	2
drug reduction/ withdrawal, poor compliance	2
multiple sclerosis	5
remote cerebrovascular disease, brain injury	7
hydrocephalus	8
alcohol abuse	10
drug overdose	11
head trauma	12
cryptogenic	12
brain tumor	16
metabolic: sodium imbalance	17
metabolic disorders	22
acute cerebrovascular disease	26
CNS-infection: acute	33
anoxia	65

AGE: score one stratum

age A (reference: 11)	EMSE-points
21-30	1
31-40	2
41-50	3
51-60	5
61-70	7
71-80	8
>80	10

EEG: score only worst stratum

EEG E (reference 13, 14)	EMSE-points
burst suppression (spontaneous)	60
ASIDs	40
LPDs	40
GPDs	40
no LPDs, GPDs or ASIDs	0

COMORBIDITY: score each disease

comorbidity C (reference: 16)	EMSE-points
myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes	10
hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor including leukemia/ lymphoma	20
moderate or severe liver disease	30
metastatic solid tumor, AIDS	60

Version history

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