HUMAN SUBJECTS SAFETY – PROJECT 3 – BIOMARKERS OF HUMAN EPILEPTOGENESIS AFTER TRAUMATIC BRAIN INJURY

IRB Approval: This study is approved by the UCLA IRB (IRB#13-001457-CR-00001).

Study Population: 300 patients with moderate-severe TBI (GCS 3-12) aged 6-100, admitted to ICUs. The studies will be performed across experienced centers capable of high resolution monitoring including cEEG monitoring. The 13 centers include UCLA, UCSD, Yale, MGH/Harvard, Columbia, U Miami, U Pittsburgh, U Cincinnati, U Maryland, Phoenix Children's, Johns Hopkins, Royal Melbourne, Addenbrooke's Cambridge University. See power calculations for justification of sample size. This group of subjects will be used for SA1-4.

Study Type: This is a hypothesis driven observational study in human subjects. There is no experimental intervention. Standard of care is provided to all subjects as determined by the treating physicians at each site. All clinical study activities including MRI, cEEG, ICU physiology observations are standard of care, for which safety is well established. Depth EEG is performed with special consent regarding risks. No specified interventions are being performed based on the information garnered from these research observations.

Inclusion Criteria: TBI patients with GCS 3-12 and with hemorrhagic contusional injuries to temporal lobes ± frontal lobes. Exclusion criteria: Patients with diffuse axonal injury in the absence of hemorrhagic contusions or skull fracture, and isolated epidural hemorrhages that improve after evacuation. Ages 6-100 are eligible. Ability to undergo MRI (lack of metal, pacemaker) studies in the acute and chronic setting. Patients may have multiple trauma including long bone fractures, blunt trauma, abdominal trauma or similar. We will permit penetrating TBI if cEEG is feasible and if survival for 2 years is considered feasible, but recognize that MRI may not be feasible with some forms of penetrating trauma (we expect penetrating trauma will comprise less than 5% of patients).

Rationale and Safety for Age Range: The proposed age range from 6-100 encompasses pediatric age range. The scientific rationale is that PTE is common in pediatrics, brain development and EEG development is stable by age 6, and the TBI injury modalities in pediatric age >= 6 is similar to adults. We have avoided most of developmental issues and non-accidental trauma and anoxic injuries by excluding younger children and by setting inclusion criteria to include temporal or frontal hemorrhagic contusions. The ADAPT study will enable unique cooperation across the age spectrum for this study. Safety concerns regarding depth EEG in pediatrics will be carefully considered and we anticipate low enrollment for depth EEG, but the low numbers will be informative and scientifically justified nonetheless. Special considerations for MRI in children are noted, and most patients will be scanned while still in coma within 14 days, hence no additional risks of sedating/intubating an awake child are anticipated for this study. Drs. Bell, Robinson, and Buttram will monitor safety issues in children closely for this study.

Exclusion criteria: Symptomatic coronary artery disease, congestive heart failure, renal insufficiency with GFR < 60% of expected or Cr > 1.3, diabetes mellitus, metabolic acidosis pH < 7.34, coagulopathy INR > 1.3, or platelets < 100,000 or hematocrit < 28 mg/dl, deep venous thrombosis, AST or ALT > 1.5x upper limit of normal, serum lactate > 2 mmol/L, Sodium < 130 meq/L, pregnancy, severe liver trauma, inability to undergo MRI or PET, pre-existing neurologic disease, pre-existing seizures, pre-existing dementia, isolated anoxic brain injury. There are no restrictions to study cohort recruitment or enrollment because of gender, race, ethnicity, or socioeconomic status.

Centers, Patient Recruitment, Populations: All study activities take place within these academic medical centers that are either level 1 Trauma Centers or Trauma Referral Centers with demonstrated ability for EEG monitoring and MRI in severe TBI. Table 1 outlines the centers and investigators:

PI	Center	Center Type	Age/Annual sTBI
Vespa/ Engel	UCLA	Level 1	A, P, N=400
Hirsch/Sheth/Gilmore	Yale	Level 1	A, N=300
Bell	U Pittsburgh	Level 1	A, P, N =500
Hartings/Foreman	U Cincinnati	Level 1	A, N=400
Obrien/Morokoff	Royal Melbourne	Level 1	A, N=250
Buttram	Phoenix Childrens'	Level 1	P, N= 100

Rosenthal	MGH/Harvard	Level 1	A, N=300
Claassen	Columbia	TBI Referral	A, N=80
Badjatia	U Maryland	Level 1	A, N=1000
O'Phalen/Bullock	U Miami	Level 1	A, N= 600
Karanjia/Constantini	UCSD	Level 1	A, N=100
Menon/ Coles	Cambridge-Addenbrooke	Level 1	A, N = 400
Robertson	Johns Hopkins	Level 1	P, N=100

Each facility has the necessary equipment including cEEG monitoring, 3T MRI for fMRI and 1.5 T or 3T for structural MRI, ICU data gathering technology, and personnel to facilitate safety for research. Each facility has qualified neurosurgeons and neurointensivists to place depth EEG as described in the methods. We will use the established EpiBioS4Rx written SOPs for patient screening, recruitment, data entry, biospecimen collection, cEEG monitoring, MRI imaging, neurocognitive testing during follow up. Each center has received the necessary training to ensure safe data collection. Each center will perform a clinical standard of care follow up for TBI as part of routine medical care.

Clinical Study Protocol Grid:

Activity	< 24 hrs	Days 1-7	Day 14	1 mo	3 mo	6 mo	1 yr	2 yrs
Consent	X							
Baseline CDEs	X							
Acute daily CDEs (10 items)		X						
ICU Physiology Synopsis (summary data -25 items)		X	X					
Brain CT	X							
Blood for biomarkers		X days 1,3,5	Day 15	X	X	X		
ICU cEEG, depth EEG	X	X						
Brain MRI (multimodal with DTI and rs fMRI			X					
Telephonic follow up GOSe,QOLIE, GOAT, DRS, comorbidities assessment				X	X	X	X	X
Epilepsy Ottman (PTE) Questionnaire				X	X	X	X	X
Study outpatient sleep-awake EEG						X		
Neurocogitive Testing (Cogstate®)							X	
Standard of Care Epilepsy Confirmation Clinic, EEG, Volumetric MRI, Structured Case Report Form (if screen positive for PTE)				←				→

Abbreviations: GOSe: Glasgow Outcome score extended; GOAT: Galveston Orientation and Amnesia Test; QOLIE: Quality of Life Epilepsy test (as specific); DRS: Disability Rating Scale.

The clinical strategy as outlined above details the timing of procedures to be performed. Abbreviations: CDE: common data elements, GOSe Glasgow Outcome Score Extended, ICP: intracranial pressure, CPP: cerebral perfusion pressure.

Anticonvulsant Use: The administration of anticonvulsants is proscribed in this study. All centers have agreed to use levetiracetam as standard of care for seizure prophylaxis according to the Brain Trauma Foundation guidelines. We anticipate some variability between centers as to the anticonvulsant duration of use based on clinical events and recognize the need to document this in the database. We anticipate that given the multicenter nature of this study, the effects of variable anticonvulsant use will be mitigated by random effects,

but we will plan to capture agent and dose administration data, and use these as covariates in our statistical analysis.

Treatment of Seizures and Status Epilepticus: The clinical trials have discussed and created a common treatment framework for seizures and status epilepticus. This is derived from published guidelines (Brophy et al, 2013). The investigators have endorsed this plan.

Definitions: Seizure: >=10 secs of evolving in frequency or location of ictal discharges or >= 10 secs of >=3 Hz discharges or ictal interictal on surface with clear cut seizures on the depth; SE: >= 5 minutes of continuous seizure activity or intermittent seizures without return to baseline; Ictal interictal: spikes or periodic discharges of <3 Hz without clear evolution.

Management:

All severe TBI patients enrolled in the trial will receive seven days of seizure prophylaxis with levetiracetam 1 gm twice daily.

Isolated seizures: Increase levetiracetam to 1500 mg bid. If seizure continue, start non continuous AED that patient is not already receiving such as phenytoin load with 20 mg/kg and start 300 mg qd (alternatives are valproic acid or lacosamide).

NCSE: give ativan 4 mg iv may repeat, load phenytoin as for isolated seizures. If the patient is already on first line (i.e., levetiracetam) and second line (i.e., phenytoin) then start midazolam infusion (Loading dose: 0.2mg/kg, with 0.2 – 0.4 mg/kg boluses repeated every 5 minutes until seizures stop, up to maximum 2mg/kg; maintenance dosing: Initial rate is 0.1mg/kg/hr; dose range: 0.05mg/kg - 2.9mg/kg per hour, titrated to seizure suppression; alternatives include valproic acid if not getting already).

Ictal interictal continuum such as periodic discharges should not be treated with AEDs unless they qualify for seizure or SE definitions.

Sedation: Sedation is commonly used for patients with moderate-severe TBI. Each center will use a standard of care sedation protocol that is titrated to best treat the patient. In some cases, deep sedation to induce burst suppression will be used. Sedation will be carefully documented in the ICU Synopsis database. Each center does use interruption of sedation as part of standard of care, and these interruptions will be documented such that EEG analysis can identify these periods. Sedation during MRI will be standardized for midazolam at 2 mg/hr during the functional MRI sequence is order to minimize effects of sedation of the rsfMRI results.

Potential risks in this research:

This study is an observational biomarker study without an intervention. Standard of care treatments will be employed for all subjects. Events may be categorized as Adverse Events (AEs) if the distress felt by the subject requires termination of testing or procedure (e.g. outcomes testing, MRI). Anticipated AEs in EpiBioS4Rx include: Excessive discomfort, pain, or bruising during venipuncture; Claustrophobia or severe anxiety in the MRI; Anxiety during outcomes administration due to sensitive material discussed; Anxiety due to fear of legal discovery associated with high-risk/illegal behaviors during interview. Sedation is not being proscribed for MRI imaging, although the use of sedatives may be given for clinical indications. Blood draws will be minimized to smallest volume possible in order to prevent anemia, and estimated at 5 cc/blood draw, with a total of 7 blood draws or 35 cc of blood over 180 days.

DSMB: We will have a DSMB that will review safety reports from all subjects and will have unfettered stopping power for individual patients, study sites, and the overall study. *Data Safety Monitoring Board (DSMB):* DSMB will be an expert group of six investigators with expertise in clinical and preclinical drug trials and drug development. DSMB includes Dr. Jacqueline French, expert in clinical trials and organizer of the AED and Pipeline Conferences; Dr. Thomas Bleck, expert in neurocritical care, epilepsy and clinical trials for status epilepticus; Dr. Emilio Perucca, expert in clinical trials for new antiepileptic therapies; Dr. Patrick Kwan, expert on both clinical and preclinical antiepileptic therapy trials; Dr. Nathalie Jetté, expert on outcome assessment and clinical trials; Dr. Roy Twyman, Vice President at Janssen Research & Development and expert in preclinical antiepileptic trials and all stages of drug development. The DSMB will monitor the procedures and progress in Project 2, review the data obtained from Projects 1-3, and advise on the best and most clinically relevant decisions on study design, evaluation, prioritization and interpretation of data (biomarkers, treatment effect), selection of the treatments that will advance onto the next stage of development (Project 2, Aim 2; selection of the lead treatment to consider for future clinical trial) and the preparation of the human cohort for a possible future clinical trial. The DSMB will participate in the annual meetings of EpiBioS4Rx. Decisions on GO

/ NO GO of a treatment will be done in coordination with the PIs of Projects 1, 2 and 3 and the Public Engagement Core representatives. DSMB members will also interact via phone or emails, as needed, with the Project 2 PL (Dr. Galanopoulou) and Project 3 PL (Dr. Vespa).

Reporting Procedures: AEs will be documented in the AE section of the database. Each Site PI will be informed on a weekly basis regarding the number and nature of the AEs at their site. The DSMB will review the number and nature of AEs at each site on a monthly basis. Given that each site must reach the 80% completion of follow-up milestone, if AEs exceed 10% of site enrollment the DSMB will contact the site to discuss potential methods for reduction of AE incidence. We anticipate that acute seizures will be detected on cEEG and treatment is not specified in our research protocol. Standard of care treatment for seizures will be up to the clinical team at each site. We will record an AE based on treatment of seizures.

Other Serious Events: Any other serious events that do not meet the above criteria will be reported to the DSMB within five working days. These AEs will be recorded for individual subjects during the 12-month study period. In addition to submission as required per site IRB regulations, AE data will be analyzed quarterly and reported in the quarterly reports submitted to the PI.

Reducing Risks to human subjects: EpiBioS4Rx will use the established best practice SOPs for clinical research activities, and has an active training program for coordinators and investigators at all sites (see appendix) to ensure safety. Given these protections, we do not anticipate risk to the subject. There is potential risk from depth electrode EEG monitoring including brain hemorrhage and infection. Five of the investigators have published seminal papers (Engel, Staba, Claassen, Vespa, Hartings) on intracranial monitoring and the complication rates are very low. Nonetheless, safety will be enhanced through care screening and exclusion of coagulopathic patients, patients at risk for infection, and at risk for complications from the depth EEG procedure. Special safety considerations for depth EEG in children are acknowledged. There is potential risk from MRI. We have an established imaging core that will perform safety and quality assessments of all MRI scanners to be used in the multicenter study, including for SOP for sedation and physiological safety in the scanners. We have identified the potential risks to human subjects and taken the necessary precautions to minimize these risks. We will do this by carefully selecting subjects with low likelihood of having adverse events, using the standard of care for any diagnostic procedure and experimental intervention, and by performing strict safety monitoring. Persons with traumatic brain injury undergo a variety of such measurements and treatments in direct response to their medical condition; these characteristically include continuous bedside monitoring of numerous physiological parameters together with electronic medical records and hospital laboratory values, and neuroimaging from multiple modalities. We presently have Institutional Review Board approval for the proposed investigation.

Medical Monitoring for Risks: We will use adhere to strict inclusion and exclusion criteria, perform quality assurance on all diagnostic testing, and perform interim safety analysis using the DSMB as the monitors. A formal DSMB will be created to supervise this research and determine if any safety issues arise from any of the testing to be done.

Confidentiality: This study will identify all laboratory specimens, evaluation forms, reports, recordings, and other records that leave a site only by a Study Identification Number (SID) to maintain subject confidentiality. Each patient is assigned a unique SID; a list of patient names and any identifying information will be kept in a separate offline document to ensure patient confidentiality. All printed records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only and all computers used for this purpose will be password protected. While personal medical information may be reviewed for the purpose of verifying recorded data, clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, or the OHRP. Radiographic masking will be used to preserve confidentiality of imaging records. When the results of the research are published or discussed in conferences, no information will be included that would reveal any individual participant's identity. All study investigators will ensure that the confidentiality of personal identity and all personal medical information of study participants are maintained at all times. Additionally, all participating clinical sites will follow all privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA).