Proposed Protocol:

Title of Study: Childhood Head Trauma: A Neuroimaging Decision Rule

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Purpose: The overall objective of this study is to develop a clinical decision rule for appropriate neuroimaging of children after minor-to-moderate head trauma. The goal of the study is to create a decision rule which identifies those children in need of emergent imaging (i.e. CT scan) and treatment, while reducing the use of head CT scans in those children with minimal risk of traumatic brain injuries.

Background: Trauma is the leading cause of death in childhood [1], and traumatic brain injury (TBI) is the leading cause of death and disability due to trauma in children. [2-4] Head trauma in children results in ~ 3,000 deaths, 29,000 hospitalizations, and 400,000 emergency department (ED) visits per year in the U. S.[5] Computed tomography (CT) is routinely used in the assessment of children with head trauma, however, <10% of these CT scans are diagnostic of TBI.[6-9] In children with minor head trauma, defined by Glasgow Coma Scale (GCS) scores of 14-15, the risk of TBI is further reduced.[6, 8, 10-12] Nonetheless, children with minor head trauma account for a substantial percentage of children with TBIs.[12-15] Several studies have proposed that clinical signs and symptoms can identify children at low risk for TBI, [6, 16, 17] although others conclude that these signs and symptoms are inadequate for identifying all children with TBIs.[8, 9, 11, 14, 18] Many previous studies, however, are limited either by small sample sizes, retrospective designs, uncontrolled analyses, and non-standardized age inclusion criteria and outcome definition.

While CT is the diagnostic test of choice for evaluating children with head trauma, this procedure has disadvantages, including exposure to radiation,[19] transport of the child away from supervision in the ED, the frequent necessity for pharmacological sedation, additional health care costs, and increased time for completing the ED evaluation. In fact, the lifetime attributable cancer mortality risk for a child after a typical head CT scan is estimated at 1 per 5,000. [20] Therefore, cranial CT scans should ideally be used selectively in the ED evaluation of children with minor blunt head trauma. Because the results of previous studies have failed to identify individual predictors or combinations of predictors that characterize a group of children at minimal risk of TBI, variation exists in clinicians' practice patterns regarding CT use in this setting.[21, 22] Published guidelines acknowledge the limitations of available data and highlight the need for larger, prospective studies on this topic.[7, 23-25] In addition, federal agencies involved with EMSC have identified broad areas in need of more research, including clinical aspects of pediatric emergency care, outcome measures, and cost-effectiveness (EMSC PA NUMBER: PA-01-044, 2001). In addition, two recent consensus panels identified minor trauma[26], and specifically TBI[27], as high priority areas in need of study.

Investigators at UC Davis, including the PI of the current proposal, recently published a 3-year prospective study of pediatric head trauma. In this study, we developed highly sensitive decision rules, with excellent negative predictive values for identifying children with TBIs defined by two separate criteria.[28]

1. Need of acute intervention (defined by neurosurgical intervention, a neurological deficit, use of anti-epileptic medication > 7 days, or hospitalization for $\geq$ 2 nights), or
2. A positive CT (contusion, hemorrhage/hematoma or cerebral edema).

As this was a pilot study, however, we were limited by the numbers of patients with TBIs, particularly in children with minor head trauma (GCS 14-15).

We now seek to derive decision rules for TBI in a multicenter study of children with non-trivial blunt head trauma evaluated in the ED who have GCS scores of 14-15. This study has been funded in full by the Maternal and Child Health Bureau (MCHB) and the Emergency Medical Services for Children (EMSC) federal program of the Health Resources and Services Administration.
Procedure: This is a prospective multicenter observational study of children < 18 years with blunt head trauma. The goal of this study is to develop a highly accurate decision rule for TBI in children with minor head trauma. This study has been endorsed by the Pediatric Emergency Care Applied Research Network (PECARN), a network created by the EMSC program and the MCHB. The goal of this network is to conduct high priority multi-institutional research into the prevention and management of acute illnesses and injuries in children. PECARN is comprised of four regional multi-institutional nodes, with a total of 25 hospital EDs from around the country among these nodes. PECARN hospitals evaluate approximately 808,000 children in their EDs on an annual basis, and thus serve as fertile ground for studying the epidemiology and management of many acute illnesses and injuries in children.

The current study is divided into two phases, the ED phase and the follow-up phase.

Emergency Department Phase

ED physicians will evaluate patients and findings will be recorded onto a standardized data sheet prior to CT scan (if obtained).

Findings recorded onto the data collection tool will include historical and physician examination findings such as:

- history of LOC
- mechanism of injury
- use of helmets
- amnesia
- seizure
- vomiting (number, timing, ED course)
- headache (intensity, diffuse vs. at site of injury, ED course)
- dizziness
- indications for CT, if obtained
- findings of altered mental status (including the GCS for children > 2 years or the pediatric GCS[29] for children $\leq$ 2 years; ED course)
- focal neurological deficits
- signs of skull fracture, and scalp trauma
- fontanelle characteristics
- clinician suspicion of alcohol or drug intoxication
- clinician suspicion of brain injury

During the ED phase no interventions outside of routine clinical care will be preformed; patient care will not be changed from the standard of care. The physician in charge of the patient in the ED will determine whether to perform a CT. No CT will be completed solely for study purposes. If a CT scan is performed, the scan will be interpreted by a local site radiologist in the course of clinical care. We will use this interpretation for the purposes of study CT outcome. However, a small number of patients will likely have an inconclusive initial interpretation of the cranial CT scan. In this situation, in which the study site radiologist is unable to make a conclusive determination of TBI status on the CT scan, a de-identified copy of that patient's CT scan will be sent (electronically or in hard-copy) to UC Davis for final review and definitive interpretation by the senior pediatric radiologist study co-investigator (Dr. Gorges). This will typically be weeks to months after the patient was cared for in the ED, so will not affect patient care.

Follow-up Phase

During the follow-up phase we will review the charts of all hospitalized study patients to determine outcome. Outcomes recorded onto a separate data collection instrument for all patients will include:

- CT findings (if obtained)
- Complications from sedation (if performed)
- Results of other neuroimaging, if obtained
- Length of hospital stay required for head injury management
- Necessity for endotracheal intubation
- all neurosurgical procedures
- associated non-neurological injuries and diagnoses (ICD-9 codes)

Rarely, the determination of "injury in need of acute intervention" will not be able to be made by the Site PI. In these cases, the pertinent aspects of the medical record will be copied and de-identified, and the record will be referred to a study "adjudication committee" who will adjudicate the outcome at a PECARN meeting. This was also included in the funded grant, and in the study Manual of Operations.

All patients will be provided an information sheet about the study and if the patient has been discharged to home from the ED the accompanying guardian will be asked to be contacted by telephone for a follow-up survey. The information sheet will be handed to the patient's guardian by the ED faculty physician or the Emergency Medicine Research Associate. We will track the compliance with the distribution of the information sheets to the patients' guardians. We have developed several steps to ensure that the information sheet is distributed to the patients' guardians. First, we have on both the first and last page of the ED data sheet provided the physician with a reminder to hand the information sheet to the patients' guardians. Second, in the rare instances where the information sheet is not given to the guardian, we will counsel the physician on providing the information sheet to the guardians. In these instances, we will read the information sheet to the guardian at the time of telephone follow-up. If the guardian doesn't refuse, they will be contacted by a trained research assistant 1-2 weeks after ED evaluation to discuss how their child is doing. If the guardian cannot be reached by telephone in the 1-2 week time period after ED evaluation, a maximum of six telephone attempts will be made to contact the guardian up to 3 months from the initial ED evaluation. We have added a box on the data sheet that will identify guardian's who identify themselves as wishing not to be contacted for telephone follow-up. Thus guardians who determine after reading the information sheet that they do not want to be contacted will have that wish documented on the data sheet at the time of ED evaluation and will not be contacted. If the guardian decides after the ED visit that they wish not to be contacted, then they may contact the project manager and make this information clear. The contact information is stated on the information sheet. During this brief (3-5 minute) telephone call the following few questions/answers in the survey will be recorded onto the data collection instrument (*see attached questions*):

- whether the child had to return to a health-care facility for the head injury
- whether the child was subsequently diagnosed with a TBI by CT or MRI imaging
- whether the child required a neurosurgical procedure for their TBI
- whether the child required hospitalization for $\geq$ 2 nights for their head injury

If a patient discharged from the ED is unavailable by telephone, questionnaires containing the same questions will be mailed to the patient. In addition, 3 to 4 times per year we will review the county

morgue records and hospital trauma center registries and emergency department continuous quality improvement (CQI) records for the names of patients discharged from the ED who were unavailable by telephone or mail follow up, to insure that they were not subsequently diagnosed with a TBI. Finally, for those patients discharged from the ED who are unavailable by telephone, we will review their medical records to determine if subsequent hospital visits (ED or clinic) were made and if the cause of such visits were from a TBI not identified on initial ED visit.

Finally, we will mail a hospital release of information form to the parent to sign, with a short cover letter, in the in the following two rare instances:

1. A patient is hospitalized at a PECARN hospital, but is then transferred to a non-PECARN hospital.
2. A patient is discharged from the ED, but then returns with a potential complication of their head trauma to a non-PECARN hospital.

In these circumstances, we will request that the parent sign a standard hospital release of information form in order that we may obtain follow-up information from the hospital of interest.

Subject Selection: Approximately 40,000 subjects over 3 years with non-trivial head trauma from the 25 centers in PECARN will be eligible for the study. Children < 18 years presenting for the evaluation of non-trivial head trauma will be eligible for enrollment.

Exclusion criteria are the following:

1. Patients with trivial head trauma, defined by falls from ground level, or trauma resulting from walking or running into stationary objects if the only abnormal finding is a scalp laceration or contusion
2. Patients with penetrating head injuries
3. Patients having undergone CT scans at outside facilities prior to transport
4. Patients with injuries occurring more than 24 hours before ED presentation
5. Patients with pre-existing intracranial hematomas

Potential Risks and Benefits: There are no major risks associated with participating in this study, as this is an observational study and no therapeutic intervention is being tested. There is a minor risk of loss of confidentiality, as the subject's name will be written on a data collection sheet. All patient identifiers, however, will be removed from the *analytical* database after study completion (*see below*). The benefit from this study is that we will gain substantial evidence on which to base decisions about CT scan use in the future. Radiation exposure to future head-injured children will be reduced and lives will be spared from radiation-induced malignancies.

<u>Protection Against Risks</u>

The data collection tool will not be part of the medical record and will be stored in a locked cabinet in the investigator's office. Data will be entered at each site onto a secure, encrypted, password-protected virtual private network (VPN) connecting to a secure, password-protected database at a computer server at the data management center at the University of Utah. At the Data Management Center, the electronic data submission will generate a database containing patient identifiers such as birthdates, hospital identifiers, etc. These data will be preserved at the end of data collection as an encrypted

archive file on a CD in a fireproof safe. To prepare the *analytical* database, the Data Management Center will encrypt these patient and institution identifiers so that the analytical database will be free of patient identifiers. This analytical database will meet patient confidentiality standards under the Health Insurance Portability and Accountability Act (HIPAA). This database will be the only one available for the analysis of the current and future derivative studies. We will maintain the confidentiality of the data at all times, as dictated under HIPAA.

Cost to Subject: There will be no cost to the subject for participating in this study.

Disclosure of Personal and Financial Interest in the Research Study and Sponsor: Investigators have no financial interest above standard contractual agreements in this research study.

Consent Process: All patients eligible for this study will be provided an information sheet (see attached) describing the ongoing study, and the guardians of patients discharged from the ED will be informed that they will be contacted for a brief telephone follow-up survey (see attached). Unless the parent/guardian refuses, they will receive a telephone call survey from a research assistant 1-2 weeks after ED discharge to discuss their child's status as described above.

Because this is a minimal risk study with no therapeutic interventions (and the study's only patient intervention is a brief follow-up telephone survey of parents/guardians of patients discharged home from the ED), we are requesting waiver from written informed consent for this study.

We are requesting this waiver for both "parts" of this study. The first part is that of data gathering in the ED of all patients, and from the medical record of those children who are hospitalized. The second part is the telephone follow-up survey of the parents/guardians of those children discharged home from the ED.

We are requesting this waiver from written informed consent for several reasons, as described below.

Part 1: ED and hospital data gathering waiver:

Because ED and hospitalization data for purposes of this study are gathered routinely during the evaluation of a child with head trauma, and this is an observational study with no therapeutic intervention, we feel that this aspect of the study (i.e. ED and hospital data gathering) meets federal waiver criteria:

This part of the study meets criteria for waiver under 45 CFR 46.116 (d), because it involves 1) no more than minimal risk to the patient, 2) the waiver would not adversely affect the rights and welfare of the subjects, 3) the research could not be practicably carried out without the waiver, and 4) the subjects (guardians) will be provided with study information (at the time of the ED visit).

As described in the section entitle "Protection Against Risks" above, we will be protecting the resulting database to maintain patient confidentiality.

Guardians will frequently be unable to provide written informed consent because they may be physically injured (or emotionally traumatized) in the same traumatic event, or may be absent at the time of initial ED evaluation if the patient is transported alone by ambulance. From the UC Davis

pilot data, ~ 35% of subjects will be victims of motor vehicle collisions. The parents of many of those children will be seriously injured and/or treated at different hospitals than the child and thus will not be available for consent. Furthermore, as patients will be presenting to the ED after traumatic events, many will have conditions such as severe pain and decreased levels of consciousness, which will prevent written informed assent from being obtained. In addition, approximately 50% of the enrolled patients will be younger than 8 years old (based on our pilot data), and too young to provide written assent.

Without this waiver the scientific rigor and generalizability of this minimal-risk, yet very important, observational study would be compromised. If informed consent is required, patient enrollment is likely to be substantially biased and enrollment reduced and highly selective: patients would be enrolled only when parents are present or non-traumatized, and only in the event that the ED physicians have time to obtain written consent. In addition, the data sheet must be completed prior to knowledge of the cranial CT scan results if a CT is obtained. Delaying enrollment until a guardian is available would likely eliminate a large percentage of eligible patients because the results of the cranial CT scan would be known prior to the guardian becoming available. Therefore, the study would be prohibitively difficult to perform and scientifically compromised without waiver of consent for ED and hospital data gathering. All PECARN centers need to enroll the maximum percentage of eligible patients to limit these potential enrollment biases and achieve the sample size needs of this study.

Part 2: Telephone follow up of guardians/parents of children discharged from the ED (see attached):

The second part of this study is the telephone follow-up survey of parents/guardians of children discharged to home from the ED. We are requesting waiver of consent from this aspect of the study as well because it meets other the federal regulations for waiver from written informed consent.

All patients discharged home from the ED will be provided an information sheet about the study indicating that the accompanying guardian will be contacted by telephone for follow-up. Unless the guardian refuses, they will be contacted by a trained research assistant 1-2 weeks after ED evaluation. During this brief (3-5 minute) telephone call the following few questions/answers will be recorded onto the data collection form:

- whether the child had to return to a health-care facility for the head injury
- whether the child was subsequently diagnosed with a TBI by CT or MRI imaging
- whether the child required a neurosurgical procedure for their TBI
- whether the child required hospitalization for their head injury

If a patient discharged from the ED is unavailable by telephone, questionnaires containing the same questions will be mailed to the patient. In this survey, we are attempting to insure that we have not missed any important injuries. We believe it meets criteria for waiver under the following regulations:

a. Under 45 CFR 46.117 (c) category 2 “An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.”

This waiver category would apply to the few simple follow-up questions in the telephone survey.

b. Under 45 CFR 46.101 (b) category 2, waiver of consent can also be extended to “Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), *survey procedures*, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.”

The follow-up telephone survey involves only the patient’s parents/guardians. We will not be contacting the child.

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