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Challenges enrolling children into traumatic brain injury trials: An observational study

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ABSTRACT

OBJECTIVES

In preparation for a clinical trial of therapeutic agents for children with moderate-to-severe blunt traumatic brain injuries (TBIs) in emergency departments (EDs), we conducted this feasibility study to 1) determine the number and clinical characteristics of eligible children, 2) determine the timing of patient and guardian arrival to the ED, and 3) describe the heterogeneity of TBIs on computed tomography (CT) scans.

METHODS

We conducted a prospective observational study at 16 EDs of children ≤ 18 years of age presenting with blunt head trauma and Glasgow Coma Scale (GCS) scores of 3-12. We documented the number of potentially eligible patients, timing of patient and guardian arrival, patient demographics and clinical characteristics, severity of injuries, and cranial CT findings.

RESULTS

We enrolled 295 eligible children at the 16 sites over 6 consecutive months. Cardiac arrest and non-survivable injuries were the most common characteristics that would exclude patients from a future trial. Most children arrived within 2 hours of injury, but most guardians did not arrive until 2-3 hours after the injury. There was a substantial range in types of TBIs, with subdural hemorrhages being the most common.

CONCLUSION

Enrolling children with moderate-to-severe TBI into time sensitive clinical trials will require large numbers of sites, meticulous preparation and coordination, and will prove challenging to obtain informed consent given the timing of patient and guardian arrival. The Federal Exception from Informed Consent for Emergency Research will be an important consideration for enrolling these children.

INTRODUCTION

Background

Traumatic brain injury (TBI) is the leading cause of death and permanent disability from trauma in children.[1,2] Among children 0-14 years in the United States, TBI results in an estimated 2,600 deaths, 37,000 hospitalizations and more than 500,000 emergency department (ED) visits.[3,4] Despite the frequency of TBI, its substantial impact on the health of children, and decades of research on the topic, there are no proven effective treatments for TBI.[5-7]

Many previous therapeutic trials for TBI in both children and adults have failed for several reasons, including: 1) the small number of patients with moderate-to-severe TBI available to be studied at any one center, 2) the heterogeneity of TBIs, and difficulty in controlling for this heterogeneity, 3) the variability in intra- and inter-institutional approaches to the treatment of patients with TBIs, 4) the difficulty in enrolling subjects within the therapeutic window of a treatment, and 5) ethical and regulatory obstacles associated with research in emergency settings, including the difficulty in obtaining timely written informed consent.[5-9] In addition, legal guardians are frequently not available in the narrow therapeutic window of potential therapies. Therefore, the Federal Exception from Informed Consent (EFIC) (21 CFR 50.24) may be necessary to study time sensitive interventions in a clinical trial.[10-12] Pre-clinical work has shown that the sooner (many) therapies are delivered to patients with TBIs, the better the outcomes. (REFS) There is an ongoing international multicenter pragmatic trial of tranexamic acid (TXA) for TBI in adults (CRASH III) where patients are randomized to TXA therapy within 8 hours of injury.[1314] In this international trial, patients who are incapable of giving consent in emergency situations are considered an exception to the general rule of informed consent per the Declaration of Helsinki.[14,15] There have been other recent large interventional ED-based trials of progesterone for TBI in adults (ProTECT III and SyNAPSe) worth noting (and both were stopped for futility) .[16,17] In ProTECT III, study drug was administered to adult patients within a 4-hour window using EFIC.[16] There are several examples of pediatric TBI trials, that failed to accrue sufficient numbers of children due to several factors such as limited numbers of eligible children at any one site, difficulties with informed consent, and arrival of subjects outside the therapeutic window of the study intervention.[5,8] The obstacles to successful pediatric TBI trials have not been sufficiently addressed or overcome. Given the history of prior unsuccessful pediatric TBI trials, it is necessary to conduct pretrial feasibility planning work to maximize the likelihood of a successful trial.[5,6,8,18]

Conducting large clinical trials in head-injured children is difficult and requires a multidisciplinary approach.[5,19] The Pediatric Emergency Care Applied Research Network (PECARN) was established to overcome the barriers of conducting research pertaining to acutely ill and injured children during all phases of emergency care and has a history of successful completion of large multicenter clinical trials.[20-27] Due to the promising pre-clinical and phase II studies for the use of progesterone for adult TBI, PECARN investigators were funded to conduct feasibility planning for a clinical trial of progesterone and other promising agents for TBI in children.[28] In this manuscript we report a prospective observational feasibility study of children with moderate-to-severe TBI presenting to 16 pediatric EDs across the US.

The goals of this study were to 1) determine the number and clinical characteristics of children with moderate-to-severe TBI at each participating site, 2) determine the timing of patient and guardian arrival to the ED to provide informed consent within the therapeutic windows of different interventions, and 3) describe the heterogeneity of TBIs on computed tomography (CT) scans.

METHODS

Study design and setting

We conducted a prospective observational study at 16 level-one pediatric trauma center EDs in PECARN. During the 9-month study period (July 2011 – Mar 2012) each site collected data on all potential eligible patients for 6 consecutive months.

Population

We prospectively enrolled children up to their 18th birthdays who presented to the ED after blunt head trauma with Glasgow Coma Scale (GCS) scores of 3-12 (i.e. moderate-to-severe TBI).

Study data collection

We collected clinical data using a study case report form including information about patient demographics, mechanisms of injury, clinical presentation including GCS, and time of arrival of patient and legal guardian. (See appendix 1 study case report form) All site PIs and research coordinators were trained on study methods using a combination of web-based presentations and conference calls before the start of patient enrollment.

Clinicians and research staff completed most case report forms prospectively. To minimize missed enrollment of eligible children, research staff screened daily for all patients with blunt head trauma and GCS scores of 3-12, then identified and retrospectively enrolled eligible children who had been missed. Physicians and research coordinators also recorded time of arrival of legally-authorized guardians. The purpose of recording guardian arrival time was to estimate a time window in which written informed consent could likely be obtained from a guardian in a future interventional trial. We asked site investigators to identify the best way to record the time of arrival of the legal guardian in advance of study initiation. Some sites recorded time of arrival from their trauma record and other sites used the time of arrival as recorded by social work. The site principal investigator (PI) or research staff member obtained the information from the treating clinician or from the medical records and did not approach the parent or patient for any information. Site research coordinators entered the data into an electronic data capture system maintained at the PECARN data center at the University of Utah.

To determine the spectrum of TBIs, each site submitted cranial CT findings for each patient enrolled in the study. The study PIs (RS, NK) reviewed radiology reports, classified and adjudicated study CT findings. For children with normal cranial CT scans, we asked site PIs to verify whether there was indeed a history of blunt head trauma; if there was no history of head trauma, these children were excluded from the database. Three children met this exclusion criterion.

Study definitions

In this analysis we used the following study definitions:

- Best GCS score: This was the best GCS that the patient had during their ED stay;
- Moderate TBI: GCS 9-12 inclusive;
- Severe TBI: GCS 3-8 inclusive;
- Non-survivable injury: This was based on the clinical judgment of the ED treating physician;
- Hypotension: Documented systolic blood pressure (SBP) below 90mmHg for patients > 10 years, <70mmHg + (age in years x 2) for patients 1- 10 years and < 70mmHg for patients < 1 year;

- Hypoxia: Documented oxygen saturation of < 90% for at least 15 consecutive minutes;
- Potential Abusive Head Trauma: Assault documented as the mechanism of injury in a patient < 3 years-old.

Human subjects protection

As this was a minimal risk study, and because it was not practical to request informed consent from each patient, we requested a waiver of informed consent. There was no interaction with the patients or guardians, and the scientific validity of the study was dependent on capturing the information from the entire population of children with moderate-to-severe TBI at each participating site. We gathered information both prospectively and retrospectively (for missed patients).

Data analysis

We prepared data summaries using SAS software (version 9.4, SAS Institute Inc., Cary, NC).

RESULTS

We enrolled 295 children with blunt head trauma and GCS scores of 3-12 during the study period at the 16 EDs. All eligible patients were captured. The cumulative total of all pediatric ED visits to the 16 participating EDs during the study period was approximately 483,426.

Table 1 describes patient demographics and mechanisms of injury, stratified by best GCS score in the ED. Of note, most enrolled patients were boys, and motor vehicle collisions (MVCs) were the most common mechanism of injury. One-half of the patients were transferred from another hospital to the participating ED. Of note, 180 (61%) children were intubated at the time of the best GCS in the ED, making neurological assessment difficult. In addition, 23% (67/295) of enrolled children received intracranial pressure (ICP) monitoring, including only one-third (59/196) of the severely injured.

We enrolled between 5 and 34 patients per ED over the 6-month period. Figure 1 shows the overall ED volume of each site over the 6-month study period and numbers of patients enrolled per site. The number of eligible patients was not related to overall ED volume of individual

institutions. Importantly, 77 (26%) of the 295 head-injured children in our study met one or more potential exclusion criteria for a future trial of TBI therapy.[3,6,21] Clinical characteristics that would make patients potentially ineligible for a future TBI trial are described in Table 2. The most common among these were cardiac arrest requiring cardiopulmonary resuscitation (CPR) prior to arrival to the ED and non-survivable injury determined in the ED. Age-adjusted hypotension was noted in 9% of patients, hypoxia in 4% and potential abusive head trauma in 6 % (as noted by the mechanism "assault" for children younger than 3 years).

Table 3 shows the timing of arrival of the child and the legal guardian after the time of injury. This result was stratified by whether the child was transferred from another hospital to the PECARN hospital, or whether the child arrived from the field to the PECARN hospital. Overall most children with TBIs arrived within 1-2 hours of their injuries, however, most parents/guardians did not arrive until 2-3 hours or later after the injury (and some guardians [n=8; 3%] did not arrive at all). Of importance, 50% of children were transferred from another hospital and only 44% of transferred children arrived within 2-3 hours of their injury; most of their guardians did not arrive until 4-5 hours after injury, which has substantial implications for informed consent for time-sensitive therapies. We also looked at timing of guardian arrival based on mechanism of injury and GCS score and we found that a higher percentage of guardians arrived 3 or more hours after injury for the more severely injured children and for children involved in MVCs.

The description and distribution of TBIs on CT are provided in Table 4. There was great heterogeneity in types of TBIs, with subdural hemorrhage being the most common intra-cranial injury, followed by subarachnoid hemorrhage. Of note, one-third of CT scans were normal.

DISCUSSION

In this study we documented the number of children with moderate-to-severe TBIs presenting to individual EDs in PECARN and demonstrated great variation in numbers between sites. In addition, up to one-quarter of these children might be excluded from a clinical trial because they met potential exclusion criteria. When we considered only those children with severe TBIs, less than one-third subsequently had ICP monitors placed. Furthermore, we found a mismatch

between the time of the patients' arrival and that of their guardians, with most patients arriving in the treating ED within 1-2 hours of their injuries and most guardians not arriving 2-3 hours or later after the injuries. Importantly, guardians of children who were transferred from other hospitals took twice as long to arrive to the study hospitals than non-transferred children's' guardians. We also showed great heterogeneity of TBIs on CT and up to one-third of children had normal initial CT scans.

Notably, we also found that the number of potential future study patients does not correlate with total ED patient volume, highlighting the differences in the types of patients seen between pediatric EDs. There was substantial variation in the numbers of patients with moderate-to-severe TBI presenting to individual pediatric trauma centers and this variation was not related to overall ED volume. This demonstrates that site selection is critical to reach adequate sample sizes in future interventional trials of TBI in children. This issue may partially account for the lack of adequate patient accrual in prior pediatric TBI trials.[5-8]

We collected data on controversial potential exclusion criteria for pediatric TBI trials (Table 2). These include age-adjusted hypotension, hypoxia and suspected abusive head trauma. Prior studies have typically excluded children with these conditions for fear of biasing the sample given that outcomes after TBI have been shown to be worse after a single episode of hypotension or hypoxia.[5,8,29] The patient history in children with suspected abusive head trauma may be unreliable, and it may not be possible to accurately determine the time of injury. Despite these issues, and given both the lack of any proven effective treatments for pediatric TBI and the number of children with TBIs who suffer from hypotension, hypoxia or abusive head trauma, one may argue about the ethics of excluding these children from a future clinical trial of a promising therapeutic agent for TBI.

Published guidelines recommend ICP monitoring for the management of children with severe TBIs.[30] In the current study, however, we found that less than one-third of children presenting to the ED with GCS scores of 8 or less subsequently had ICP monitors placed during their hospital stay. Prior studies have shown significant between-site variations in ICP monitor placement in children with severe TBIs.[31] The relative infrequency of ICP monitoring in our

study may reflect that head-injured children with low GCS scores due to intubation with pharmacological sedation and paralysis may have been found not to have severe TBI when the sedation and paralysis were reversed; the relative infrequency of ICP monitor use may also reflect practice variation between physicians. Therefore, in future pediatric TBI clinical trials conducted in the ED it may be important to consider timely reversal of paralysis and sedation to determine the true GCS score, or to accurately determine the GCS score in the prehospital setting prior to paralysis, sedation and intubation. Future trials will also require standardization of care of these patients beyond the study intervention. The lower-than-expected number of children with severe TBI and subsequent ICP monitor placement in the current study may also reflect the number of children in the cohort who had non- survivable injuries identified in the ED and therefore did not have ICP monitors placed.

We found that one-half of all children with moderate-to-severe head injuries were transferred from another facility and that approximately one-half of children were present in the study ED within 2 hours of injury. The time lag between injury and arrival to the definitive treatment hospital is potentially concerning for future interventional trials given the time-sensitive nature of many TBI therapies to be tested. Of greater concern, however, is that only approximately one-half of legal guardians were present in the ED within 2-3 hours of their child's injury. Our finding that most guardians of children transferred from other hospitals took 4-5 hours to arrive and that one-half of the children in our study were transferred is concerning given the time-sensitive nature of interventions in many TBI trials. Guardian arrival time starts the window in which written informed consent could be obtained. This has important implications for future pediatric trials of therapies for TBI if these therapies have narrow windows of efficacy. In particular, delayed availability of a legal guardian argues for use of the Federal Exception from Informed Consent for Emergency Research in pediatric trials of TBI therapies. [11,12] Furthermore, even in cases where the guardian is at the bedside in a timely manner, the level of stress and anxiety over the critical condition of their children may preclude guardians from providing true informed consent. PECARN is currently conducting a trial of second-line therapy in children with refractory status epilepticus using the Federal Exception from Informed Consent.[32] Although many of the patients' guardians are present at the bedside, the life threatening nature of status epilepticus, the need for timely treatment and the level of stress and anxiety among

guardians makes it difficult to have a true informed consent discussion before initiating treatment. Similarly the ProTECT III trial of progesterone for TBI in adults was conducted using EFIC.[16]

The most common injury mechanisms in the study were MVCs. With this particular mechanism, many guardians may have been victims as well and taken to adult facilities for treatment. Furthermore, approximately one-half of the children in our study were transported from another hospital for definitive treatment and many ambulances do not allow guardians to travel with their children. Lack of guardian availability in the ED for children with TBIs has been demonstrated in other studies[10], again arguing for EFIC.[11] In the CRASH I trial (which included children older than 16 years of age) sites which had to obtain written informed consent took significantly longer to randomize patients and ultimately to administer study drug (3 hours versus 4 hours).[33,34]

Our study also showed substantial heterogeneity of intra-cranial injuries among children with moderate-to-severe TBIs. The implications of this may be important, as certain interventions may target specific types of intracranial injuries. For example, progesterone has been shown to have several different mechanisms of action and, therefore, adult progesterone trials have typically enrolled patients with all types of intracranial injuries which could theoretically benefit from the actions of progesterone (recent negative trials notwithstanding).[16,35] However, future trials of targeted therapies may need to enroll children with specific injury types, such as TXA for intracranial hemorrhage.[36-40] In our cohort, intracranial hemorrhage was the most common type of brain injury on CT, accounting for approximately one-half of enrolled patients.

Surprisingly, even after site PI review of enrolled patients (all with moderate-to-severe TBIs) one-third of these children had normal initial CT scans. If future trials require abnormal CT scans as an inclusion criterion, a substantial proportion of potentially eligible patients with normal initial CT scans may be missed. We did not evaluate, however, how many of these children had MRI or CT scans performed later which demonstrated serious injuries not apparent on the initial CT scans. In addition, it may take some time to determine the final, definitive CT interpretation when a child presents to the ED with TBI. Therefore, waiting for the CT scan to be definitively

interpreted to determine eligibility for a TBI trial could significantly delay patient enrollment, and threaten administration of trial drug during the therapeutic window.

This study had some limitations. We conducted the study using a waiver of informed consent; therefore, we didn't approach parents to assess their willingness to consent to a future interventional trial for TBI. In order to define who would be truly eligible we would have needed to intervene and reverse paralysis and sedation for each intubated patient to evaluate who had a GCS of 3 because of pharmacological sedation/paralysis rather than severe TBI. However, the need to get informed consent would bias our ability to capture all patients for the outcomes of interest. As a result, by using GCS alone, we likely overestimated the available number of children for a future TBI trial. In addition, we did not follow patients to document outcomes because of the same concerns about informed consent potentially biasing the main objectives of the study. Documenting outcomes of TBI was also beyond the scope of our study, in which the aim was to quantify the number of patients eligible for a future trial, and assess time of patient and guardian arrival in order to prepare for patient/guardian consent in future TBI trials. We were able to do this without consent, and captured all patients. Outcomes of moderate-severe TBI in children are known, and were not the focus here. In addition, although some patients were enrolled retrospectively, the limited dataset was highly objective (e.g. time of patient arrival, GCS score) and this allowed us to capture all eligible patients. We also found that some sites have no standardized documentation of parental presence. Therefore each site determined the best method for documenting this presence for their setting. This is a source of documentation that should be standardized across all pediatric trauma centers.

Future trials of TBI in children will require inclusion of many high-enrolling sites, may require international collaboration, and will likely take several years to perform. However, if such definitive studies result in demonstrating novel therapies to be effective for the treatment of moderate-to-severe TBI in children, the costs and efforts will be greatly outweighed by the reduction of morbidity and mortality, and quality life-years saved.

CONCLUSIONS

In summary, we identified the number, timing of arrival, and important clinical and CT characteristics of potentially eligible children with moderate-to-severe TBIs for future clinical trials of novel therapeutic agents. Enrolling children with moderate-to-severe TBIs into clinical trials is challenging and will require large numbers of sites, meticulous preparation and coordination, and will prove challenging with regards to timing of patient and guardian arrival. Given these challenges, the Federal Exception from Informed Consent for Emergency Research will be an important consideration for timely enrollment of children into TBI clinical trials.

REFERENCES Don't capitalize first words in title (See Nishijima reference at end). Need to standardize journal abbreviations as well

1. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths 2002-2006. *CDC, Atlanta GA.* 2010.
2. Schneier AJ, Shields BJ, Hostetler SG, Xiang H, Smith GA. Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. *Pediatrics.* Aug 2006;118(2):483-492.
3. Center for Disease Control and Prevention. Rates of TBI-related Deaths by Age Group — United States, 2001–2010. Accessed from: http://www.cdc.gov/traumaticbraininjury/data/rates_deaths_byage.html. Date of Access: 8/19/2016.
4. Centers for Disease Control and Prevention. Get the Stats on Traumatic Brain Injury in the United States. Available from: http://www.cdc.gov/traumaticbraininjury/pdf/bluebook_factsheet-a.pdf. Date of Access: 8/19/2016.
5. Natale JE, Joseph JG, Pretzlaff RK, Silber TJ, Guerguerian AM. Clinical trials in pediatric traumatic brain injury: unique challenges and potential responses. *Dev Neurosci.* 2006;28(4-5):276-290.
6. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *J Neurotrauma.* May 2002;19(5):503-557.
7. Menon DK. Unique challenges in clinical trials in traumatic brain injury. *Crit Care Med.* Jan 2009;37(1 Suppl):S129-135.
8. Adelson PD, Wisniewski SR, Beca J, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. *Lancet neurology.* Jun 2013;12(6):546-553.

9. Duhaime A, Alario A, Lewander W, et al. Head injury in very young children: mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age. *Pediatrics.* Aug 1992;90(2 Pt 1):179-185.

10. Holmes JF, Holubkov R, Kuppermann N. Guardian availability in children evaluated in the emergency department for blunt head trauma. *Acad Emerg Med.* Jan 2009;16(1):15-20.

11. Food and Drug Administration. Guidance for institutional review boards, clinical investigators and sponsors: Exception from Informed Consent Requirements for Emergency Medicine Research. March 2011. http://www.fda.gov/downloads /RegulatoryInformation/Guidances /UCM249673.pdf. Accessed January 6, 2015, 2015.

12. Code of Federal Reguations Title 21: Exception from informed consent requirements for emergency research. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=50.24. Date of Access: 8/19/2016.

13. CRASH 3-Clinical Randomisation of an Antifibrolytic in Significant Head Injury. Available from: http://crash3.lshtm.ac.uk/. Date of access 8/10/2016.

14. Dewan Y, Komolafe EO, Mejia-Mantilla JH, et al. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials.* 2012;13:87.

15. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA : the journal of the American Medical Association.* Nov 27 2013;310(20):2191-2194.

16. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *The New England journal of medicine.* Dec 25 2014;371(26):2457-2466.

17. Skolnick BE, Maas AI, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. *The New England journal of medicine.* Dec 25 2014;371(26):2467-2476.

18. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *The New England journal of medicine.* Jun 5 2008;358(23):2447-2456.

19. Stanley RM, Bonsu BK, Zhao W, Ehrlich PF, Rogers AJ, Xiang H. US estimates of hospitalized children with severe traumatic brain injury: implications for clinical trials. *Pediatrics.* Jan 2012;129(1):e24-30.

20. Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet.* Oct 3 2009;374(9696):1160-1170.

21. Corneli HM, Zorc JJ, Mahajan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *The New England journal of medicine.* Jul 26 2007;357(4):331-339.

22. Moler FW, Donaldson AE, Meert K, et al. Multicenter cohort study of out-of-hospital pediatric cardiac arrest. *Crit Care Med.* Jan 2011;39(1):141-149.

23. Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. *JAMA : the journal of the American Medical Association.* Apr 23-30 2014;311(16):1652-1660.

24. Holmes JF, Wisner DH, McGahan JP, Mower WR, Kuppermann N. Clinical prediction rules for identifying adults at very low risk for intra-abdominal injuries after blunt trauma. *Annals of emergency medicine.* Oct 2009;54(4):575-584.

25. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children. *New England Journal of Medicine.* 2015.

26. Badaki-Makun O, Scott JP, Panepinto JA, et al. Intravenous magnesium for pediatric sickle cell vaso-occlusive crisis: methodological issues of a randomized controlled trial. *Pediatric blood & cancer.* Jun 2014;61(6):1049-1054.

27. Tzimenatos L, Kim E, Kuppermann N. The Pediatric Emergency Care Applied Research Network: a history of multicenter collaboration in the United States. *Pediatric emergency care.* Jan 2015;31(1):70-76.

28. Stanley R. EMSC Targeted Issues Grant Funding: Progesterone for Traumatic Brain Injury in Children: Planning a Safety and Efficacy Trial. Available at http://www.emscresources.org/historicalgrants/searchResults.php?stateSearch=MI Date Accessed 06-12-15.

29. Vavilala MS, Bowen A, Lam AM, et al. Blood pressure and outcome after severe pediatric traumatic brain injury. *The Journal of trauma.* Dec 2003;55(6):1039-1044.

30. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* Jan 2012;13 Suppl 1:S1-82.

31. Van Cleve W, Kernic MA, Ellenbogen RG, et al. National variability in intracranial pressure monitoring and craniotomy for children with moderate to severe traumatic brain injury. *Neurosurgery.* Nov 2013;73(5):746-752; discussion 752; quiz 752.

32. The Established Status Epilepticus Treatment Trial. Available from: http://nett.umich.edu/clinical-trials/esett. Date of Access: 8/19/2016.

33. Maas AI, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics.* Jan 2010;7(1):115-126.

34. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet.* Oct 9-15 2004;364(9442):1321-1328.

35. Skolnick BE, Maas AI, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. *The New England journal of medicine.* Dec 25 2014;371(26):2467-2476.

36. Pusateri AE, Weiskopf RB, Bebarta V, et al. Tranexamic acid and trauma: current status and knowledge gaps with recommended research priorities. *Shock.* Feb 2013;39(2):121-126.

37. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC emergency medicine.* 2013;13:20.

38. Crash-2 Collaborators IBS. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *Bmj.* 2011;343:d3795.

39. Beno S, Ackery AD, Callum J, Rizoli S. Tranexamic acid in pediatric trauma: why not? *Critical care.* Jul 2 2014;18(4):313.

40. Nishijima DK, Monuteaux MC, Faraoni D, et al. Tranexamic acid use in United States children's hospitals. *J Emerg Med.* Jun 2016;50(6):868-874 e861.

Table 1. Results: Demographics and Injury Data (Using Best GCS in the ED)

Characteristics	N (%)	GCS 3-8 Severe TBI	GCS 9-12 Moderate TBI
Number Enrolled	295	196	57
Patient age in years (Median, Range)	6.4 (0.1-17.9)	6.9 (0.1-17.9)	4.3 (0.1-17.9)
Gender			
Male	190 (64%)	124 (63%)	34 (60%)
Female	105 (36%)	72 (37%)	23 (40%)
Race			
White	162 (55%)	115 (59%)	26 (46%)
Black	65 (22%)	36 (18%)	18 (32%)
Other	20 (7%)	12 (6%)	3 (5%)
Unknown	48 (16%)	33 (17%)	10 (18%)
Ethnicity			
Hispanic	38 (13%)	24 (12%)	9 (16%)
Non-Hispanic	212 (72%)	144 (73%)	34 (60%)
Unknown	45 (15%)	28 (14%)	14 (25%)
Mechanism of Injury			
MVC	88 (30%)	74 (38%)	9 (16%)

Fall	69 (23%)	29 (15%)	26 (46%)
Pedestrian/Bike Injury	36 (12%)	23 (12%)	8 (14%)
Assault	21 (7%)	17 (9%)	4 (7%)
Sports Related	22 (7%)	11 (6%)	1 (2%)
Other	20 (7%)	10 (5%)	6 (11%)
Multiple	34 (12%)	28 (14%)	3 (5%)
Unknown	5 (2%)	4 (2%)	0 (0%)
Intubated at the time of best GCS in the ED	180 (61%)	168 (86%)	12 (21%)
Transfer from another hospital	148 (50%)	113 (58%)	20 (35%)
ICP Monitoring	67 (23%)	59 (30%)	8 (14%)
MRI Obtained	89 (30%)	70 (36%)	13 (23%)

Table 2. Reasons for Potential Exclusions for Future Interventional Trial and Percentage of Patients that Met Each Criterion

Reason	**N (%)**
Died in the ED	15 (5%)
Cardiac arrest with CPR prior to arrival	35 (12%)
Non survivable injury determined in ED	32 (11%)
Spinal cord injury resulting in neurologic deficit	19 (6%)
Hypotension (age-defined)	27 (9%)
Hypoxia (O2 sat < 90% for > 15 mins)	11 (4%)

Penetrating head injury	10 (3%)
Potential abusive head trauma	17 (6%)
Total number of patients that met one or more exclusion criteria	77 (26%)

Table 3. Results: Time from Injury to Arrival in ED

	Overall Cumulative frequency (%)		**Patients not transferred from another hospital Cumulative frequency (%)**		**Patients transferred from another hospital Cumulative frequency (%)**	
Hours After Injury	**Patient (N=284)**	**Guardian (N=284)**	**Patient (N=141)**	**Guardian (N=142)**	**Patient (N=143)**	**Guardian (N=142)**
0-1 hour	100 (35%)	59 (21%)	97 (69%)	57 (40%)	3 (2%)	2 (1%)
>1-2 hours	161 (57%)	112 (39%)	133 (94%)	96 (68%)	28 (20%)	16 (11%)
>2-3 hours	199 (70%)	145 (51%)	136 (96%)	107 (75%)	63 (44%)	38 (27%)
>3-4 hours	228 (80%)	183 (64%)	138 (98%)	122 (86%)	90 (63%)	61 (43%)
>4-5 hours	247 (87%)	212 (75%)	139 (99%)	127 (89%)	108 (76%)	85 (60%)
>5-6 hours	262 (92%)	232 (82%)	139 (99%)	132 (93%)	123 (86%)	100 (70%)
>6-7 hours	268 (94%)	239 (84%)	139 (99%)	132 (93%)	129 (90%)	107 (75%)

Table 4. Description of Types of Intracranial Injuries by CT

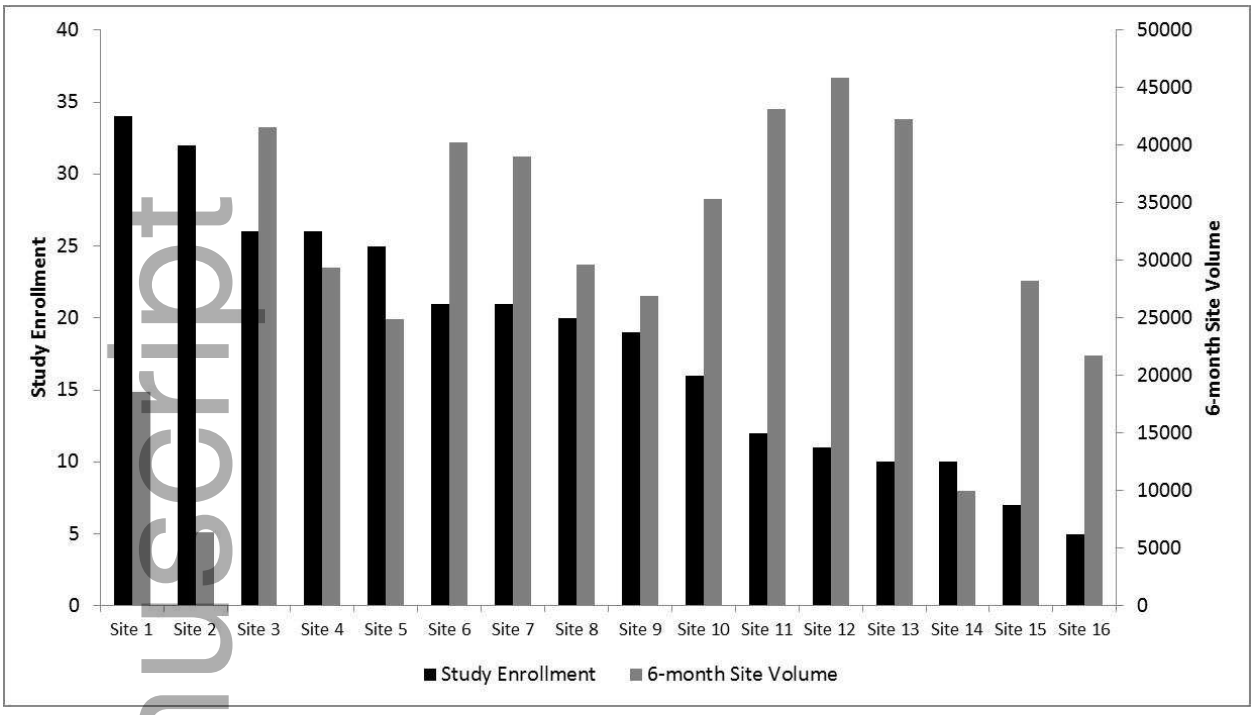
Type of Injury	N (%)
Number of patients with CT scans	282
Number of patients with normal ED CT scans	92 (32.6%)
Total number of patients with any CT finding*	190
Traumatic findings on CT	
Skull fracture	106 (55.8%)
Subdural hematoma	75 (39.5%)
Cerebral edema	56 (29.5%)
Basilar skull fracture	51 (26.8%)
Subarachnoid hemorrhage	48 (25.3%)
Cerebral hemorrhage	33 (17.4%)
Pneumocephalus	31 (16.3%)
Midline shift /shift of brain structures	30 (15.8%)
Cerebral contusion	26 (13.7%)
Extra-axial hematoma	21 (11.1%)
Epidural hematoma	17 (8.9%)
Herniation	15 (7.9%)
Intraventricular hemorrhage	14 (7.4%)

Other traumatic findings#	18 (8.9%)

* Of the 190 with CT findings, 44 had one finding and 146 had more than one finding

Diffuse axonal injury (3.7%), Shear injury (1.6%), and Traumatic infarction (1.6%), Diastasis of the skull (0.5%)

Figure 1. Study Enrollment and ED Volume per Site over 6 Months



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ABSTRACT

OBJECTIVES

In preparation for a clinical trial of therapeutic agents for children with moderate-to-severe blunt traumatic brain injuries (TBIs) in emergency departments (EDs), we conducted this feasibility study to 1) determine the number and clinical characteristics of eligible children, 2) determine the timing of patient and guardian arrival to the ED, and 3) describe the heterogeneity of TBIs on computed tomography (CT) scans.

METHODS

We conducted a prospective observational study at 16 EDs of children ≤ 18 years of age presenting with blunt head trauma and Glasgow Coma Scale (GCS) scores of 3-12. We documented the number of potentially eligible patients, timing of patient and guardian arrival, patient demographics and clinical characteristics, severity of injuries, and cranial CT findings.

RESULTS

We enrolled 295 eligible children at the 16 sites over 6 consecutive months. Cardiac arrest and non-survivable injuries were the most common characteristics that would exclude patients from a future trial. Most children arrived within 2 hours of injury, but most guardians did not arrive until 2-3 hours after the injury. There was a substantial range in types of TBIs, with subdural hemorrhages being the most common.

CONCLUSION

Enrolling children with moderate-to-severe TBI into time sensitive clinical trials will require large numbers of sites, meticulous preparation and coordination, and will prove challenging to obtain informed consent given the timing of patient and guardian arrival. The Federal Exception from Informed Consent for Emergency Research will be an important consideration for enrolling these children.

INTRODUCTION

Background

Traumatic brain injury (TBI) is the leading cause of death and permanent disability from trauma in children.[1,2] Among children 0-14 years in the United States, TBI results in an estimated 2,600 deaths, 37,000 hospitalizations and more than 500,000 emergency department (ED) visits.[3,4] Despite the frequency of TBI, its substantial impact on the health of children, and decades of research on the topic, there are no proven effective treatments for TBI.[5-7]

Many previous therapeutic trials for TBI in both children and adults have failed for several reasons, including: 1) the small number of patients with moderate-to-severe TBI available to be studied at any one center, 2) the heterogeneity of TBIs, and difficulty in controlling for this heterogeneity, 3) the variability in intra- and inter-institutional approaches to the treatment of patients with TBIs, 4) the difficulty in enrolling subjects within the therapeutic window of a treatment, and 5) ethical and regulatory obstacles associated with research in emergency settings, including the difficulty in obtaining timely written informed consent.[5-8] In addition, legal guardians are frequently not available in the narrow therapeutic window of potential therapies. Therefore, the Federal Exception from Informed Consent (EFIC) (21 CFR 50.24) may be necessary to study time sensitive interventions in a clinical trial.[9-11] Pre-clinical work has shown that the sooner (many) therapies are delivered to patients with TBIs, the better the outcomes. There is an ongoing international multicenter pragmatic trial of tranexamic acid (TXA) for TBI in adults (CRASH III) where patients are randomized to TXA therapy within 8 hours of injury.[12,13] In this international trial, patients who are incapable of giving consent in emergency situations are considered an exception to the general rule of informed consent per the Declaration of Helsinki.[13,14] There have been other recent large interventional ED-based trials of progesterone for TBI in adults (ProTECT III and SyNAPSe) worth noting (and both were stopped for futility).[15,16] In ProTECT III, study drug was administered to adult patients within a 4-hour window using EFIC.[15] There are several examples of pediatric TBI trials that failed to accrue sufficient numbers of children due to several factors such as limited numbers of eligible children at any one site, difficulties with informed consent, and arrival of subjects outside the therapeutic window of the study intervention.[5,8] The obstacles to successful pediatric TBI trials have not been sufficiently addressed or overcome. Given the history of prior unsuccessful pediatric TBI trials, it is necessary to conduct pretrial feasibility planning work to maximize the likelihood of a successful trial.[5,6,8]

Conducting large clinical trials in head-injured children is difficult and requires a multidisciplinary approach.[5,17] The Pediatric Emergency Care Applied Research Network (PECARN) was established to overcome the barriers of conducting research pertaining to acutely ill and injured children during all phases of emergency care and has a history of successful completion of large multicenter clinical trials.[18-25] Due to the promising pre-clinical and phase II studies for the use of progesterone for adult TBI, PECARN investigators were funded to conduct feasibility planning for a clinical trial of progesterone and other promising agents for TBI in children.[26] In this manuscript we report a prospective observational feasibility study of children with moderate-to-severe TBI presenting to 16 pediatric EDs across the US.

The goals of this study were to 1) determine the number and clinical characteristics of children with moderate-to-severe TBI at each participating site, 2) determine the timing of patient and guardian arrival to the ED to provide informed consent within the therapeutic windows of different interventions, and 3) describe the heterogeneity of TBIs on computed tomography (CT) scans.

METHODS

Study design and setting

We conducted a prospective observational study at 16 level-one pediatric trauma center EDs in PECARN. During the 9-month study period (July 2011 – Mar 2012) each site collected data on all potential eligible patients for 6 consecutive months.

Population

We prospectively enrolled children up to their 18th birthdays who presented to the ED after blunt head trauma with Glasgow Coma Scale (GCS) scores of 3-12 (i.e. moderate-to-severe TBI).

Study data collection

We collected clinical data using a study case report form including information about patient demographics, mechanisms of injury, clinical presentation including GCS, and time of arrival of patient and legal guardian. (See appendix 1 study case report form) All site PIs and research coordinators were trained on study methods using a combination of web-based presentations and conference calls before the start of patient enrollment.

Clinicians and research staff completed most case report formd prospectively. To minimize missed enrollment of eligible children, research staff screened daily for all patients with blunt head trauma and GCS scores of 3-12, then identified and retrospectively enrolled eligible children who had been missed. Physicians and research coordinators also recorded time of arrival of legally-authorized guardians. The purpose of recording guardian arrival time was to estimate a time window in which written informed consent could likely be obtained from a guardian in a future interventional trial. We asked site investigators to identify the best way to record the time of arrival of the legal guardian in advance of study initiation. Some sites recorded time of arrival from their trauma record and other sites used the time of arrival as recorded by social work. The site principal investigator (PI) or research staff member obtained the information from the treating clinician or from the medical records and did not approach the parent or patient for any information. Site research coordinators entered the data into an electronic data capture system maintained at the PECARN data center at the University of Utah.

To determine the spectrum of TBIs, each site submitted cranial CT findings for each patient enrolled in the study. The study PIs (RS, NK) reviewed radiology reports, classified and adjudicated study CT findings. For children with normal cranial CT scans, we asked site PIs to verify whether there was indeed a history of blunt head trauma; if there was no history of head trauma, these children were excluded from the database. Three children met this exclusion criterion.

Study definitions

In this analysis we used the following study definitions:

- Best GCS score: This was the best GCS that the patient had during their ED stay;
- Moderate TBI: GCS 9-12 inclusive;
- Severe TBI: GCS 3-8 inclusive;
- Non-survivable injury: This was based on the clinical judgment of the ED treating physician;
- Hypotension: Documented systolic blood pressure (SBP) below 90mmHg for patients > 10 years, <70mmHg + (age in years x 2) for patients 1- 10 years and < 70mmHg for patients < 1 year;

- Hypoxia: Documented oxygen saturation of < 90% for at least 15 consecutive minutes;
- Potential Abusive Head Trauma: Assault documented as the mechanism of injury in a patient < 3 years-old.

Human subjects protection

As this was a minimal risk study, and because it was not practical to request informed consent from each patient, we requested a waiver of informed consent. There was no interaction with the patients or guardians, and the scientific validity of the study was dependent on capturing the information from the entire population of children with moderate-to-severe TBI at each participating site. We gathered information both prospectively and retrospectively (for missed patients).

Data analysis

We prepared data summaries using SAS software (version 9.4, SAS Institute Inc., Cary, NC).

RESULTS

We enrolled 295 children with blunt head trauma and GCS scores of 3-12 during the study period at the 16 EDs. All eligible patients were captured. The cumulative total of all pediatric ED visits to the 16 participating EDs during the study period was approximately 483,426.

Table 1 describes patient demographics and mechanisms of injury, stratified by best GCS score in the ED. Of note, most enrolled patients were boys, and motor vehicle collisions (MVCs) were the most common mechanism of injury. One-half of the patients were transferred from another hospital to the participating ED. Of note, 180 (61%) children were intubated at the time of the best GCS in the ED, making neurological assessment difficult.
In addition, 23% (67/295) of enrolled children received intracranial pressure (ICP) monitoring, including only one-third (59/196) of the severely injured.

We enrolled between 5 and 34 patients per ED over the 6-month period. Figure 1 shows the overall ED volume of each site over the 6-month study period and numbers of patients enrolled per site. The number of eligible patients was not related to overall ED volume of individual

institutions. Importantly, 77 (26%) of the 295 head-injured children in our study met one or more potential exclusion criteria for a future trial of TBI therapy.[3,6] Clinical characteristics that would make patients potentially ineligible for a future TBI trial are described in Table 2. The most common among these were cardiac arrest requiring cardiopulmonary resuscitation (CPR) prior to arrival to the ED and non-survivable injury determined in the ED. Age-adjusted hypotension was noted in 9% of patients, hypoxia in 4% and potential abusive head trauma in 6 % (as noted by the mechanism "assault" for children younger than 3 years).

Table 3 shows the timing of arrival of the child and the legal guardian after the time of injury. This result was stratified by whether the child was transferred from another hospital to the PECARN hospital, or whether the child arrived from the field to the PECARN hospital. Overall most children with TBIs arrived within 1-2 hours of their injuries, however, most parents/guardians did not arrive until 2-3 hours or later after the injury (and some guardians [n=8; 3%] did not arrive at all). Of importance, 50% of children were transferred from another hospital and only 44% of transferred children arrived within 2-3 hours of their injury; most of their guardians did not arrive until 4-5 hours after injury, which has substantial implications for informed consent for time-sensitive therapies. We also looked at timing of guardian arrival based on mechanism of injury and GCS score and we found that a higher percentage of guardians arrived 3 or more hours after injury for the more severely injured children and for children involved in MVCs.

The description and distribution of TBIs on CT are provided in Table 4. There was great heterogeneity in types of TBIs, with subdural hemorrhage being the most common intra-cranial injury, followed by subarachnoid hemorrhage. Of note, one-third of CT scans were normal.

DISCUSSION

In this study we documented the number of children with moderate-to-severe TBIs presenting to individual EDs in PECARN and demonstrated great variation in numbers between sites. In addition, up to one-quarter of these children might be excluded from a clinical trial because they met potential exclusion criteria. When we considered only those children with severe TBIs, less than one-third subsequently had ICP monitors placed. Furthermore, we found a mismatch

between the time of the patients' arrival and that of their guardians, with most patients arriving in the treating ED within 1-2 hours of their injuries and most guardians not arriving 2-3 hours or later after the injuries. Importantly, guardians of children who were transferred from other hospitals took twice as long to arrive to the study hospitals than non-transferred children's' guardians. We also showed great heterogeneity of TBIs on CT and up to one-third of children had normal initial CT scans.

Notably, we also found that the number of potential future study patients does not correlate with total ED patient volume, highlighting the differences in the types of patients seen between pediatric EDs. There was substantial variation in the numbers of patients with moderate-to-severe TBI presenting to individual pediatric trauma centers and this variation was not related to overall ED volume. This demonstrates that site selection is critical to reach adequate sample sizes in future interventional trials of TBI in children. This issue may partially account for the lack of adequate patient accrual in prior pediatric TBI trials.[5-8]

We collected data on controversial potential exclusion criteria for pediatric TBI trials (Table 2). These include age-adjusted hypotension, hypoxia and suspected abusive head trauma. Prior studies have typically excluded children with these conditions for fear of biasing the sample given that outcomes after TBI have been shown to be worse after a single episode of hypotension or hypoxia.[5,8,27] The patient history in children with suspected abusive head trauma may be unreliable, and it may not be possible to accurately determine the time of injury. Despite these issues, and given both the lack of any proven effective treatments for pediatric TBI and the number of children with TBIs who suffer from hypotension, hypoxia or abusive head trauma, one may argue about the ethics of excluding these children from a future clinical trial of a promising therapeutic agent for TBI.

Published guidelines recommend ICP monitoring for the management of children with severe TBIs.[28] In the current study, however, we found that less than one-third of children presenting to the ED with GCS scores of 8 or less subsequently had ICP monitors placed during their hospital stay. Prior studies have shown significant between-site variations in ICP monitor placement in children with severe TBIs.[29] The relative infrequency of ICP monitoring in our

study may reflect that head-injured children with low GCS scores due to intubation with pharmacological sedation and paralysis may have been found not to have severe TBI when the sedation and paralysis were reversed; the relative infrequency of ICP monitor use may also reflect practice variation between physicians. Therefore, in future pediatric TBI clinical trials conducted in the ED it may be important to consider timely reversal of paralysis and sedation to determine the true GCS score, or to accurately determine the GCS score in the prehospital setting prior to paralysis, sedation and intubation. Future trials will also require standardization of care of these patients beyond the study intervention. The lower-than-expected number of children with severe TBI and subsequent ICP monitor placement in the current study may also reflect the number of children in the cohort who had non- survivable injuries identified in the ED and therefore did not have ICP monitors placed.

We found that one-half of all children with moderate-to-severe head injuries were transferred from another facility and that approximately one-half of children were present in the study ED within 2 hours of injury. The time lag between injury and arrival to the definitive treatment hospital is potentially concerning for future interventional trials given the time-sensitive nature of many TBI therapies to be tested. Of greater concern, however, is that only approximately one-half of legal guardians were present in the ED within 2-3 hours of their child's injury. Our finding that most guardians of children transferred from other hospitals took 4-5 hours to arrive and that one-half of the children in our study were transferred is concerning given the time-sensitive nature of interventions in many TBI trials. Guardian arrival time starts the window in which written informed consent could be obtained. This has important implications for future pediatric trials of therapies for TBI if these therapies have narrow windows of efficacy. In particular, delayed availability of a legal guardian argues for use of EFIC in pediatric trials of TBI therapies.[10,11] Furthermore, even in cases where the guardian is at the bedside in a timely manner, the level of stress and anxiety over the critical condition of their children may preclude guardians from providing true informed consent. PECARN is currently conducting a trial of second-line therapy in children with refractory status epilepticus using EFIC.[30] Although many of the patients' guardians are present at the bedside, the life threatening nature of status epilepticus, the need for timely treatment and the level of stress and anxiety among guardians makes it difficult to have a true informed consent discussion before initiating treatment.

Similarly the ProTECT III trial of progesterone for TBI in adults was conducted using the EFIC.[15]

The most common injury mechanisms in the study were MVCs. With this particular mechanism, many guardians may have been victims as well and taken to adult facilities for treatment. Furthermore, approximately one-half of the children in our study were transported from another hospital for definitive treatment and many ambulances do not allow guardians to travel with their children. Lack of guardian availability in the ED for children with TBIs has been demonstrated in other studies[9], again arguing for EFIC.[10] In the CRASH I trial (which included children older than 16 years of age) sites which had to obtain written informed consent took significantly longer to randomize patients and ultimately to administer study drug (3 hours versus 4 hours).[31,32]

Our study also showed substantial heterogeneity of intra-cranial injuries among children with moderate-to-severe TBIs. The implications of this may be important, as certain interventions may target specific types of intracranial injuries. For example, progesterone has been shown to have several different mechanisms of action and, therefore, adult progesterone trials have typically enrolled patients with all types of intracranial injuries which could theoretically benefit from the actions of progesterone (recent negative trials notwithstanding).[15,33] However, future trials of targeted therapies may need to enroll children with specific injury types, such as TXA for intracranial hemorrhage.[34-38] In our cohort, intracranial hemorrhage was the most common type of brain injury on CT, accounting for approximately one-half of enrolled patients.

Surprisingly, even after site PI review of enrolled patients (all with moderate-to-severe TBIs) one-third of these children had normal initial CT scans. If future trials require abnormal CT scans as an inclusion criterion a substantial proportion of potentially eligible patients with initial normal CT scans may be missed. We did not evaluate, however, how many of these children had MRI or CT scans performed later which demonstrated serious injuries not apparent on the initial CT scans. In addition, it may take some time to determine the final, definitive CT interpretation when a child presents to the ED with TBI. Therefore, waiting for the CT scan to be definitively interpreted to determine eligibility for a TBI trial could significantly delay patient enrollment, and threaten administration of trial drug during the therapeutic window.

This study had some limitations. We conducted the study using a waiver of informed consent; therefore, we didn't approach parents to assess their willingness to consent to a future interventional trial for TBI. In order to define who would be truly eligible we would have needed to intervene and reverse paralysis and sedation for each intubated patient to evaluate who had a GCS of 3 because of pharmacological sedation/paralysis rather than severe TBI. However, the need to get informed consent would bias our ability to capture all patients for the outcomes of interest. As a result, by using GCS alone we likely overestimated the available number of children for a future TBI trial. In addition, we did not follow patients to document outcomes because of the same concerns about informed consent potentially biasing the main objectives of the study. Documenting outcomes of TBI was also beyond the scope of our study, in which the aim was to quantify the number of patients eligible for a future trial, and assess time of patient and guardian arrival in order to prepare for patient/guardian consent in future TBI trials. We were able to do this without consent, and captured all patients. Outcomes of moderate-severe TBI in children are known, and were not the focus here. In addition, although some patients were enrolled retrospectively, the limited dataset was highly objective (e.g. time of patient arrival, GCS score) and this allowed us to capture all eligible patients. We also found that some sites have no standardized documentation of parental presence. Therefore each site determined the best method for documenting this presence for their setting. This is a source of documentation that should be standardized across all pediatric trauma centers.

Future trials of TBI in children will require inclusion of many high-enrolling sites, may require international collaboration, and will likely take several years to perform. However, if such definitive studies result in demonstrating novel therapies to be effective for the treatment of moderate-to-severe TBI in children, the costs and efforts will be greatly outweighed by the reduction of morbidity and mortality, and quality life-years saved.

CONCLUSIONS

In summary, we identified the number, timing of arrival, and important clinical and CT characteristics of potentially eligible children with moderate-to-severe TBIs for future clinical

trials of novel therapeutic agents. Enrolling children with moderate-to-severe TBIs into clinical trials is challenging and will require large numbers of sites, meticulous preparation and coordination, and will prove challenging with regards to timing of patient and guardian arrival. Given these challenges, the Federal Exception from Informed Consent for Emergency Research will be an important consideration for timely enrollment of children into TBI clinical trials.

REFERENCES

1. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths 2002-2006. *CDC, Atlanta GA.* 2010.
2. Schneier AJ, Shields BJ, Hostetler SG, Xiang H, Smith GA. Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. *Pediatrics.* Aug 2006;118(2):483-492.
3. Center for Disease Control and Prevention. Rates of TBI-related Deaths by Age Group — United States, 2001–2010. Accessed from: http://www.cdc.gov/traumaticbraininjury/data/rates_deaths_byage.html. Date of Access: 8/19/2016.
4. Centers for Disease Control and Prevention. Get the Stats on Traumatic Brain Injury in the United States. Available from: http://www.cdc.gov/traumaticbraininjury/pdf/bluebook_factsheet-a.pdf. Date of Access: 8/19/2016.
5. Natale JE, Joseph JG, Pretzlaff RK, Silber TJ, Guerguerian AM. Clinical trials in pediatric traumatic brain injury: unique challenges and potential responses. *Dev Neurosci.* 2006;28(4-5):276-290.
6. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *J Neurotrauma.* May 2002;19(5):503-557.
7. Menon DK. Unique challenges in clinical trials in traumatic brain injury. *Crit Care Med.* Jan 2009;37(1 Suppl):S129-135.
8. Adelson PD, Wisniewski SR, Beca J, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. *Lancet neurology.* Jun 2013;12(6):546-553.
9. Holmes JF, Holubkov R, Kuppermann N. Guardian availability in children evaluated in the emergency department for blunt head trauma. *Acad Emerg Med.* Jan 2009;16(1):15-20.

10. Food and Drug Administration. Guidance for institutional review boards, clinical investigators and sponsors: Exception from Informed Consent Requirements for Emergency Medicine Research. March 2011. http://www.fda.gov/downloads /RegulatoryInformation/Guidances /UCM249673.pdf. Accessed January 6, 2015, 2015.

11. Code of Federal Reguations Title 21: Exception from informed consent requirements for emergency research. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=50.24. Date of Access: 8/19/2016.

12. CRASH 3-Clinical Randomisation of an Antifibrolytic in Significant Head Injury. Available from: http://crash3.lshtm.ac.uk/. Date of access 8/10/2016.

13. Dewan Y, Komolafe EO, Mejia-Mantilla JH, et al. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials.* 2012;13:87.

14. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA : the journal of the American Medical Association.* Nov 27 2013;310(20):2191-2194.

15. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *The New England journal of medicine.* Dec 25 2014;371(26):2457-2466.

16. Skolnick BE, Maas AI, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. *The New England journal of medicine.* Dec 25 2014;371(26):2467-2476.

17. Stanley RM, Bonsu BK, Zhao W, Ehrlich PF, Rogers AJ, Xiang H. US estimates of hospitalized children with severe traumatic brain injury: implications for clinical trials. *Pediatrics.* Jan 2012;129(1):e24-30.

18. Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet.* Oct 3 2009;374(9696):1160-1170.

19. Moler FW, Donaldson AE, Meert K, et al. Multicenter cohort study of out-of-hospital pediatric cardiac arrest. *Crit Care Med.* Jan 2011;39(1):141-149.

20. Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. *JAMA : the journal of the American Medical Association.* Apr 23-30 2014;311(16):1652-1660.

21. Holmes JF, Wisner DH, McGahan JP, Mower WR, Kuppermann N. Clinical prediction rules for identifying adults at very low risk for intra-abdominal injuries after blunt trauma. *Annals of emergency medicine.* Oct 2009;54(4):575-584.

22. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children. *New England Journal of Medicine.* 2015.

23. Badaki-Makun O, Scott JP, Panepinto JA, et al. Intravenous magnesium for pediatric sickle cell vaso-occlusive crisis: methodological issues of a randomized controlled trial. *Pediatric blood & cancer.* Jun 2014;61(6):1049-1054.

24. Tzimenatos L, Kim E, Kuppermann N. The Pediatric Emergency Care Applied Research Network: a history of multicenter collaboration in the United States. *Pediatric emergency care.* Jan 2015;31(1):70-76.

25. Corneli HM, Zorc JJ, Mahajan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *The New England journal of medicine.* Jul 26 2007;357(4):331-339.

26. Stanley R. EMSC Targeted Issues Grant Funding: Progesterone for Traumatic Brain Injury in Children: Planning a Safety and Efficacy Trial. Available at http://www.emscresources.org/historicalgrants/searchResults.php?stateSearch=MI Date Accessed 06-12-15.

27. Vavilala MS, Bowen A, Lam AM, et al. Blood pressure and outcome after severe pediatric traumatic brain injury. *The Journal of trauma.* Dec 2003;55(6):1039-1044.

28. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* Jan 2012;13 Suppl 1:S1-82.

29. Van Cleve W, Kernic MA, Ellenbogen RG, et al. National variability in intracranial pressure monitoring and craniotomy for children with moderate to severe traumatic brain injury. *Neurosurgery.* Nov 2013;73(5):746-752; discussion 752; quiz 752.

30. The Established Status Epilepticus Treatment Trial. Available from: http://nett.umich.edu/clinical-trials/esett. Date of Access: 8/19/2016.

31. Maas AI, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. *Neurotherapeutics : the Journal of the American Society for Experimental NeuroTherapeutics.* Jan 2010;7(1):115-126.

32. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet.* Oct 9-15 2004;364(9442):1321-1328.

33. Skolnick BE, Maas AI, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. *The New England journal of medicine.* Dec 25 2014;371(26):2467-2476.

34. Pusateri AE, Weiskopf RB, Bebarta V, et al. Tranexamic acid and trauma: current status and knowledge gaps with recommended research priorities. *Shock.* Feb 2013;39(2):121-126.

35. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC emergency medicine.* 2013;13:20.

36. Crash-2 Collaborators IBS. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *Bmj.* 2011;343:d3795.

37. Beno S, Ackery AD, Callum J, Rizoli S. Tranexamic acid in pediatric trauma: why not? *Critical care.* Jul 2 2014;18(4):313.

38. Nishijima DK, Monuteaux MC, Faraoni D, et al. Tranexamic acid use in United States children's hospitals. *The Journal of emergency medicine.* Jun 2016;50(6):868-874 e861.

Table 1. Results: Demographics and Injury Data (Using Best GCS in the ED*)

Characteristics	**N (%)**	**Best GCS 3-8 Severe TBI**	**Best GCS 9-12 Moderate TBI**
Number Enrolled	295	196	57
Patient age in years (Median, Range)	6.4 (0.1-17.9)	6.9 (0.1-17.9)	4.3 (0.1-17.9)
Gender			
Male	190 (64%)	124 (63%)	34 (60%)
Female	105 (36%)	72 (37%)	23 (40%)
Race			
White	162 (55%)	115 (59%)	26 (46%)
Black	65 (22%)	36 (18%)	18 (32%)
Other	20 (7%)	12 (6%)	3 (5%)
Unknown	48 (16%)	33 (17%)	10 (18%)
Ethnicity			
Hispanic	38 (13%)	24 (12%)	9 (16%)
Non-Hispanic	212 (72%)	144 (73%)	34 (60%)
Unknown	45 (15%)	28 (14%)	14 (25%)
Mechanism of Injury			
MVC	88 (30%)	74 (38%)	9 (16%)
Fall	69 (23%)	29 (15%)	26 (46%)
Pedestrian/Bike Injury	36 (12%)	23 (12%)	8 (14%)
Assault	21 (7%)	17 (9%)	4 (7%)
Sports Related	22 (7%)	11 (6%)	1 (2%)
Other	20 (7%)	10 (5%)	6 (11%)

Multiple	34 (12%)	28 (14%)	3 (5%)
Unknown	5 (2%)	4 (2%)	0 (0%)
Intubated at the time of best GCS in the ED	180 (61%)	168 (86%)	12 (21%)
Transfer from another hospital	148 (50%)	113 (58%)	20 (35%)
ICP Monitoring	67 (23%)	59 (30%)	8 (14%)
MRI Obtained	89 (30%)	70 (36%)	13 (23%)

*42 subject's GCS improved to >12 in the ED therefore they are not included in columns 2 and 3

Table 2. Reasons for Potential Exclusions for Future Interventional Trial and Percentage of Patients that Met Each Criterion

Reason	N (%)
Died in the ED	15 (5%)
Cardiac arrest with CPR prior to arrival	35 (12%)
Non survivable injury determined in ED	32 (11%)
Spinal cord injury resulting in neurologic deficit	19 (6%)
Hypotension (age-defined)	27 (9%)
Hypoxia (O2 sat < 90% for > 15 mins)	11 (4%)
Penetrating head injury	10 (3%)
Potential abusive head trauma	17 (6%)
Total number of patients that met one or more exclusion criteria	77 (26%)

Table 3. Results: Time from Injury to Arrival in ED

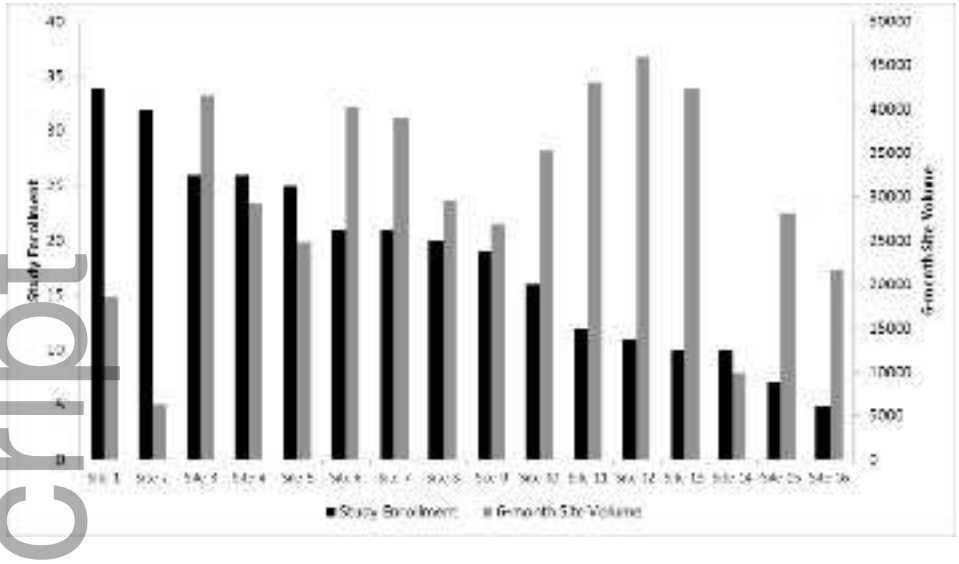
	Overall Cumulative frequency (%)		Patients not transferred from another hospital Cumulative frequency (%)		Patients transferred from another hospital Cumulative frequency (%)	
Hours After Injury	**Patient (N=284)**	**Guardian (N=284)**	**Patient (N=141)**	**Guardian (N=142)**	**Patient (N=143)**	**Guardian (N=142)**
0-1 hour	100 (35%)	59 (21%)	97 (69%)	57 (40%)	3 (2%)	2 (1%)
>1-2 hours	161 (57%)	112 (39%)	133 (94%)	96 (68%)	28 (20%)	16 (11%)
>2-3 hours	199 (70%)	145 (51%)	136 (96%)	107 (75%)	63 (44%)	38 (27%)
>3-4 hours	228 (80%)	183 (64%)	138 (98%)	122 (86%)	90 (63%)	61 (43%)
>4-5 hours	247 (87%)	212 (75%)	139 (99%)	127 (89%)	108 (76%)	85 (60%)
>5-6 hours	262 (92%)	232 (82%)	139 (99%)	132 (93%)	123 (86%)	100 (70%)
>6-7 hours	268 (94%)	239 (84%)	139 (99%)	132 (93%)	129 (90%)	107 (75%)

Table 4. Description of Types of Intracranial Injuries by CT

Type of Injury	N (%)
Number of patients with CT scans	282
Number with normal ED CT scans	92 (32.6%)
Total number of patients with any CT finding*	190
Traumatic findings on CT	
Skull fracture	106 (55.8%)
Subdural hematoma	75 (39.5%)
Cerebral edema	56 (29.5%)
Basilar skull fracture	51 (26.8%)
Subarachnoid hemorrhage	48 (25.3%)
Cerebral hemorrhage	33 (17.4%)
Pneumocephalus	31 (16.3%)
Midline shift /shift of brain structures	30 (15.8%)
Cerebral contusion	26 (13.7%)
Extra-axial hematoma	21 (11.1%)
Epidural hematoma	17 (8.9%)
Herniation	15 (7.9%)
Intraventricular hemorrhage	14 (7.4%)
Other traumatic findings#	18 (8.9%)

* Of the 190 with CT findings, 44 had one finding and 146 had more than one finding

Diffuse axonal injury (3.7%), Shear injury (1.6%), and Traumatic infarction (1.6%), Diastasis of the skull (0.5%) and other



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