A Clinical Decision Rule to Identify Children with Intra-abdominal Injuries (Abdominal Decision Rule Project)

PECARN Protocol Number 020

Pediatric Emergency Care Applied Research Network
Maternal and Child Health, Emergency Medical Services
for Children (EMSC) Program

Contents

1   Purpose

The long term objective of our research is to derive, refine, validate, disseminate and implement decision support tools to optimize the evaluation of children with blunt trauma, leading to reduced morbidity and mortality. The overall objective of this study is to develop a clinical decision rule for appropriate use of abdominal computerized tomography (CT) scanning in children with blunt torso trauma (to include the chest, abdomen and pelvis). The goal of the study is to create a decision rule that identifies those children in need of emergent CT scan and treatment, while reducing the use of abdominal CT scans in those children with minimal risk of intra-abdominal injuries (IAI). The study has been approved and is funded by the Centers for Disease Control and Prevention (1 R49 CE001002).

This study has two Specific Aims:

Specific Aim 1. To refine and internally validate a clinical decision rule that accurately and precisely identifies children at high risk of IAI in need of acute intervention. The sensitivity of this rule must be nearly 100%.

Specific Aim 2. To refine and internally validate a clinical decision rule that accurately and precisely identifies those children at near-zero risk of IAI in need of acute intervention. The negative predictive value (NPV) of this rule must be nearly 100%.

We hypothesize that application of this refined decision rule would reduce the number of overall scans that would have been obtained in the study population without missing an IAI requiring acute intervention. We will assess this by retrospectively applying the final rule to the study population database and comparing the actual observed CT scanning rate versus the rate of CT scanning recommended by the decision rule.

We anticipate that the proposed study will substantially improve the care of children in the following ways:

1. By identifying readily available predictors of IAI, we will be able to identify children at high risk of IAI needing emergent abdominal imaging and treatment. With such a decision rule, those children with IAI will be identified quickly, efficiently and reliably, and missed IAIs will

be avoided. Children with IAIs will less likely suffer mortality and morbidity from inappropriate under-diagnosis and under-treatment.

2. By identifying indicators of very low risk for IAI, we will be able to reliably identify children who do not require abdominal CT scans. In these children, we can avoid potential adverse consequences of CT, including exposure to radiation, as well as unnecessary costs and use of resources.

2 Background

Trauma is the leading cause of death in childhood.[1,2] In 2001, over 17,000 children less than 20 years of age died from traumatic injuries.[1] Although injuries to the central nervous system are the leading cause of death from blunt traumatic injury, hemorrhage (most commonly into the thoracic or abdominal cavity) is the second leading cause and accounts for 30% of blunt traumatic related deaths.[3] Nine percent of children with IAIs will ultimately die.[4] Many children with IAI have subtle findings making the diagnosis difficult; delays in diagnosis or failures to diagnose IAI result in increasing morbidity.[5–8] With the introduction of abdominal CT scanning in the late 1980s, the method of diagnostic evaluation of children with blunt torso trauma subsequently became more standardized. Abdominal CT scanning has become the diagnostic imaging technique of choice to identify IAIs in hemodynamically stable children after blunt torso trauma at both designated and non-designated trauma centers.[9,10] Abdominal CT safely decreases the level of clinical monitoring required by the injured child and positively influences the surgeons' treatment plans.[11,12] It is estimated that 1.4 million abdominal CT scans are obtained in the U.S. annually on children and $\approx$10% of these abdominal CT scans are obtained for evaluation of possible traumatic IAIs.[13]

Because of the importance of identifying children with IAI, the use of abdominal CT scan has increased substantially over the last decade.[14] Recent studies have questioned the increased utilization of abdominal CT scanning, suggesting that additional abdominal CT scanning has not improved clinical outcomes.[14,15] The development of fast helical CT scanners have added new dimensions and diagnostic possibilities, reduced the need for sedation of children undergoing CT scan, and increased the type of CT examinations that can be performed. Radiation exposure, however, has not decreased with the helical CT, and it remains high. Therefore, increased use of abdominal CT scans confers significant radiation risks.

CT scanning accounts for most (67 - 75%) of the collective effective radiation dose from diagnostic imaging, despite that only 10 - 15% of all radiographic studies are CT scans.[16,17] The most important potential risk of CT is the risk of malignancy posed by the exposure to CT radiation.[13,16,18–22] The typical radiation dose from a current pediatric abdominal CT scan is 600 times greater than that for a routine chest radiograph.[18]

Specific estimates of the risk of malignancy due to radiation exposure in children are extrapolated from data on survivors of atomic bombs during World War II.[23,24] These models include the radiation dose, the organ system exposed, age at exposure, and time from exposure. It is well known that children are more susceptible than adults to the induction of malignancy from radiation. This is related to the increased sensitivity of developing pediatric organs, as well as longer life expectancy after the exposure which provides a larger period of time in which adverse effects can be expressed. The current estimates of lifetime attributable risk of a fatal cancer from one current-generation abdominal CT scan range from 1 per 444 abdominal CT scans for infants younger than 1 year to 1 per 1,000 for those 15 years old.[13] Furthermore, for every case of fatal cancer caused by abdominal CT scans, up to three cases of non-fatal cancer will be induced.[21] Creation of a decision rule that reduces abdominal CT use in children with blunt torso trauma by 10% (given approximately 140,000 such CT scans per year) would potentially decrease the number of radiation-induced malignancies by approximately 580 cases per year, including 194 resulting in death. Although the risks of radiation-induced malignancy are measurable, they are small for any given individual. Thus CT scanning should not be avoided for those in whom medical indications exist. Nevertheless, the risk of cancer from CT scanning in children has become a recognized issue when the collective public health is considered, and has been widely publicized to practicing clinicians[22,25] and lay public.[26–28]

The National Cancer Institute (NCI) has recommended three short term measures and two long term strategies to minimize CT radiation in children.[18] These recommendations include adjustment of the radiation dosages for the size of the child, and pediatric radiologists have begun to make appropriate dosage adjustments for CT scanning.[29–32] However, the first short term recommendation from the NCI is to "perform only necessary CT examinations" and the first long term recommendation is to "encourage development and adoption of pediatric CT protocols". The results from this proposal would satisfy these recommendations from the NCI.

Investigators at UC Davis recently published a 3-year prospective study of pediatric abdominal trauma. In this pilot study, we developed a highly

sensitive decision rule, with excellent negative predictive values for identifying children with IAIs.[33] Although the decision rule derived in the pilot study demonstrates good test characteristics, for several reasons the rule needs to be refined and validated in a large, diverse cohort of injured children prior to implementation:

1. The 95% confidence intervals remain too wide for clinical use because of a relatively small sample size.

2. Variables that are potential predictors of IAI were not entered into the pilot analysis.

3. The lack of multicenter validation of the decision rule limits the ability to generalize the rule to all children with blunt abdominal trauma seen across the country. Central to the development and implementation of clinical decision rules is a requirement to refine and validate the rule in a separate population, particularly in a multicenter study.[34–36]

We address these limitations in this new multicenter study of children with blunt torso trauma evaluated in the emergency department (ED) who are hemodynamically stable. The study has been approved and is funded by the Centers for Disease Control and Prevention (1 R49 CE001002).

3   Subject Selection

Approximately 13,000 subjects with blunt torso trauma from participating centers in PECARN will be recruited for the study, over a 3 year study period. Children < 18 years old presenting for the evaluation of non-trivial abdominal trauma will be eligible for enrollment.

Inclusion Criteria:

1. Blunt torso trauma resulting from a significant mechanism of injury, such as:

   - Motor vehicle collision: high speed, ejection, or rollover
   - Automobile versus pedestrian/bicycle: automobile moderate to high speed 5mph
   - Falls greater than or equal to 20 feet in height
   - Crush injury to the torso
   - Physical assault involving the abdomen

2. Decreased level of consciousness (GCS score < 15 or below age-appropriate behavior) in association with blunt torso trauma

3. Blunt traumatic event with any of the following (regardless of the mechanism):

   - Extremity paralysis
   - Multiple long bone fractures at multiple sites (e.g. tibia and humerus fracture)

4. History or physical examination suggestive of IAI following blunt torso trauma of any mechanism (including mechanisms of injury of less severity than mentioned above)

Exclusion Criteria:

1. Penetrating trauma

2. Pre-existing neurological disorders seriously confounding physical examination assessment (e.g. profound mental retardation and/or cerebral palsy)

3. Traumatic injury occurred more than 24 hours prior to the time of presentation to the ED

4. Transfer of the patient to the participating center from an outside facility with abdominal CT or Diagnostic Peritoneal Lavage (DPL) already performed.

5. Patient is pregnant.

6. Patient has a documented IAI < 30 days prior to ED presentation.

4   Study Procedure

This is a prospective multicenter observational study of children < 18 years with blunt torso trauma. The goal of this study is to develop a highly accurate decision rule for predicting IAI in these children. This study has been endorsed by the Steering Committee of the Pediatric Emergency Care Applied Research Network (PECARN), and this study will be carried out at participating hospitals in this network.

   We have defined "injury in need of acute intervention" to be any of the following:

1. Death secondary to an IAI
2. Therapeutic intervention at laparotomy (i.e. necessary abdominal surgery)
3. Angiographic embolization of an actively bleeding abdominal organ or other abdominal vascular structure
4. Blood transfusion for anemia secondary to intra-abdominal hemorrhage from an IAI
5. Administration of intravenous fluids for $\geq$ two nights to maintain hydration in patients unable to eat or drink because of their IAI (e.g. pancreatic or duodenal injuries).

The determination of "injury in need of acute intervention" will be made by the site PI. 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 that will adjudicate the outcome at a PECARN meeting.

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

4.1   Emergency Department Phase

ED physicians will evaluate eligible patients with blunt torso trauma (chest, abdomen, and pelvic) and findings will be recorded onto a standardized data collection form prior to CT scan (if obtained).

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

- history of loss of consciousness
- mechanism of injury
- abdominal pain
- costal margin pain
- vomiting (number, timing, ED course)
- indications for CT, if obtained
- findings of altered mental status
- abdominal tenderness
- flank tenderness
- costal margin tenderness
- systolic blood pressure
- peritoneal irritation
- abdominal distention
- abdominal wall injury
- femur fracture
- thoracic or pelvic injuries
- clinician suspicion of alcohol or drug intoxication

- need for non-abdominal

surgery
- clinician suspicion of IAI

During the ED phase, *no interventions* outside of routine clinical care will be performed; patient care will not be changed from the routine care at the local site. The physician in charge of the patient in the ED will determine whether to perform any abdominal imaging including abdominal CT scan. No imaging study will be completed solely for study purposes. If an abdominal 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 abdominal CT scan. In this situation, in which the study site radiologist is unable to make a conclusive determination of IAI 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 Medical Center for final review and definitive interpretation by a senior pediatric radiologist. This will typically be weeks to months after the patient was cared for in the ED, and will not affect patient care.

Patients eligible for the study but not enrolled by the ED physician will have brief epidemiologic (age, mechanism of injury) and clinical data (ED mental status, presence or absence of IAI and abdominal CT results) abstracted from the medical record. This will ensure that enrolled patients are similar to "missed" patients, but no contact will be made with the parent or guardian of these "missed eligible" patients (eligible for enrollment but not enrolled by the ED physician).

4.2   Follow-up Phase

During the follow-up phase, site personnel will review the medical records of all eligible, hospitalized study patients to determine their clinical course and outcomes. Outcomes recorded onto a separate data collection instrument for all patients will include:

- Hospital admission or discharge from the ED
- Abdominal CT findings (if obtained)
- Complications from sedation (if performed)
- Results of other abdominal imaging, if obtained
- Length of hospital stay for IAI management
- Necessity for blood transfusion for IAI
- Necessity for IV hydration for IAI

- Necessity for angiographic embolization for hemorrhage from an IAI
- Associated non-abdominal injuries and diagnoses (ICD-9 codes)

An information sheet about the study will be provided to the child's parent, guardian, or responsible family member. If the patient has been discharged to home from the ED, the accompanying parent, guardian or responsible family member will be asked to be contacted by telephone for a follow-up survey. The information sheet will be handed to the patient's parent, guardian or responsible family member by the ED physician, the site PI, the site research assistant, or a nurse in the Emergency Department. We have developed several steps to ensure that the information sheet is distributed to the parents, guardians or responsible family members. First, we have provided the physician on both the first and last page of the ED data collection form with a reminder to hand the information sheet to the parents, guardians or responsible family members. Second, in the rare instances where the information sheet is not given to the parent, guardian or responsible family member, we will counsel the physician on the importance of providing the information sheet to the parents, guardians or responsible family members. In these instances, we will read the information sheet to the parent, guardian or responsible family member at the time of telephone follow-up.

If the parent, guardian or responsible family member does not refuse, they will be contacted by a trained research assistant 1-2 weeks after ED evaluation to ask how their child is doing. If the guardian or responsible family member cannot be reached by telephone in the time period after ED evaluation, a maximum of six telephone attempts will be made to contact the parent, guardian or responsible family member up to 3 months from the initial ED evaluation. There is a box on the ED data collection form that will identify parents, guardians, or responsible family members who identify themselves as wishing not to be contacted for telephone follow-up. Thus, parents, guardians or responsible family members who determine after reading the information sheet that they do not want to be contacted will have that wish documented on the data collection form at the time of ED evaluation, and they will not be contacted for telephone follow-up. If the parent, guardian or responsible family member 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 will be asked and the answers will be recorded onto a data collection form:

- whether the child had to return to a health-care facility for signs or symptoms of IAI
- whether the child was subsequently diagnosed with a IAI by CT
- whether the child required an abdominal surgical procedure for their IAI
- whether the child required hospitalization for their IAI

If the parent, guardian or responsible family member of a patient discharged from the ED is unavailable by telephone during the 3 month follow-up period, questionnaires containing the same questions will be mailed to the patient's home address. If the parent, guardian or responsible family member does not respond to the mail questionnaire, we will, first, review the hospital medical records of these patients who were discharged from the ED and were lost to follow-up. In this medical record review, we will determine if the patient returned to the ED or hospital clinic with signs or symptoms of IAI. If we are still unable to obtain follow-up after the medical record review, we will at regular intervals review the county morgue records, 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 follow-up, mail follow up, or medical record review to insure that they were not subsequently diagnosed with a IAI.

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

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

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

5   Statistical Analyses

We will conduct separate analyses, and potentially develop different decision rules, for each of the three IAI outcome variables:

1. IAI in need of acute intervention

2. IAI that is clinically significant

3. IAI identified on abdominal CT scan, other radiographic studies or at laparotomy

Since the usefulness of clinical decision rules depends greatly on the reliability (reproducibility of findings) of patient history and physical examination, inter-rater reliability of measures considered in the decision rule will be measured on a cohort of patients using the kappa (κ) statistic.[37,38]

5.1   Specific Aim One

Specific Aim 1. To refine and internally validate a clinical decision rule that accurately and precisely identifies children at high risk of IAI in need of acute intervention. The sensitivity of this rule must be nearly 100%.

Refining and Validating the Decision Rule.   To refine the decision rule(s), we will use binary recursive partitioning on a study population consisting of approximately 9,774 subjects. Binary recursive partitioning is a non-parametric multivariable analytic technique used to classify observations based on risk profiles for the outcome of interest, using a tree-like structure with decision "nodes."[39] These decision trees are easily interpreted by both researchers and clinicians. As the display enables users to visualize the hierarchical interaction of the variables, the clinician is able to determine the risk of the outcome for each step of the decision tree.

One of the advantages of this approach is that it automatically explores interactions between predictors that may appear in the decision tree. This is in contrast to logistic regression, in which interaction terms must be created by the investigator in order to explore interactions between predictors. Therefore, recursive partitioning allows the investigators to identify predictors that may have differential relevance in different subgroups. Another advantage of this technique is that it allows for the inclusion of more variables (and combinations of variables), in comparison with traditional logistic regression.[39] Recursive partitioning also allows for the inclusion of patients

with missing predictors. Therefore, patients with missing observations for one or more predictors are not dropped from the analysis (as they are in logistic regression analysis). If a prediction variable is missing more than 5% of the time, however, that variable will be dropped from final analyses.

We will use classification and regression tree software (CART Version 5.0; San Diego, CA: Salford Systems, 2002) to perform this analysis and will internally validate the decision rule using 10-fold cross validation. This validation technique is performed by partitioning the data into 10 strata, with each strata containing equal likelihood of the outcome. Ten different subanalyses are then performed, in which decision trees are derived from analysis of 90% of the data and tested on the remaining 10% of the data which was initially withheld. Different unique subsets of derivation and test data are used in each iteration. The average performance of these subanalyses is an estimate of how the tree derived from 100% of the data will perform on subsequent data samples and is used to determine the "best" tree.

We will enter only those clinical variables (mechanistic, historical, and physical examination variables) whose kappa statistic is greater than 0.4 into the analysis. This cutoff is chosen as it demonstrates at least, moderate agreement between the raters. We will also enter PECARN site variables as dummy variables into the analysis to explore whether any site exerts disproportionate influence in the generation of the rule.

Assessing the Accuracy of the Decision Rule. We will assess the accuracy of the rules by applying the rules to the study population and measuring the rule classification performance. This will be assessed by standard measures of accuracy (sensitivity, specificity, positive predictive values, negative predictive values, and likelihood ratios) for the presence of any variable in the rule. We will also report 95% CIs for all above measures.

Sample Size Calculations for Sensitivity of the Decision Rule. Under the assumption (based on the pilot data) that 18% of all hemodynamically stable patients with IAI will have IAI in need of acute intervention, an enrollment of approximately 877 (i.e. 164/0.187) hemodynamically stable patients with IAI of any type in the study will be needed. This translates into the need for approximately 9,774 hemodynamically stable children with blunt abdominal trauma in this study, given the estimate from the pilot study that approximately 9% of eligible children will have IAIs. This determines the size of our required sample.

An average of 693 children with IAIs are evaluated at each participating study site ED on an annual basis. Approximately 5% of these 693 patients will be transferred to the participating centers with known diagnosis of IAI and thus, are ineligible, leaving 658 eligible patients with IAI annually. Assuming an enrollment rate of 70 - 80%, approximately 461 to 526 patients with IAI will be enrolled annually at each site. Of these, 89% will be hemodynamically stable and, therefore, meet the criteria for analysis. Thus, 410 to 468 hemodynamically stable patients with IAI will be eligible and enrolled each year at each site. Therefore, the study would require 23 to 26 months of enrollment to meet the sample size requirements for sensitivity. In our previous studies developing decision support rules, up to 35% of the initially enrolled subjects are later determined to be ineligible (e.g. the CT scan was already obtained when the clinician filled out the data form), or were lost to follow-up, preventing accurate assessment of the patient's outcome. Therefore, in order to assure that we have a sufficient number of subjects with the outcome of interest (IAI), we will enroll approximately 13,000 subjects. The target enrollment of 13,000 subjects will require approximately 30 to 36 months.

5.2   Specific Aim Two

Specific Aim 2. To refine and internally validate a clinical decision rule that accurately and precisely identifies those children at near-zero risk of IAI in need of acute intervention. The negative predictive value (NPV) of this rule must be nearly 100%.

The NPV is the second critical element of the refined decision rules. Patients predicted not to have an IAI in need of acute intervention should not have an IAI in need of acute intervention (i.e. we are seeking a 100% NPV).

Sample Size Calculations for NPV of the Decision Rule.   In our pilot study, approximately 36% of the hemodynamically stable patients were identified by the decision rule as not at risk of having an IAI. It can be safely assumed that the risk of IAI requiring acute intervention among the children evaluated with CT scan would be equal to or greater than that in the group not evaluated by CT scan. Therefore, if we assume an overall minimum of 36% of children at near-zero risk, this gives approximately 3,519 children with near zero risk among the 9,774 hemodynamically stable children to be recruited. Thus, the target sample size is adequate for the purposes of Specific Aim 2.

5.3 Total Enrollment and Projected Accrual Period.

As described above, the data set target will consist of approximately 9,774 subjects, including 877 subjects with IAI. We plan to enroll up to 13,000 subjects. The additional 3,000 patients will include additional patients needed if the rate of IAI among the enrolled patients is lower than the pilot study and possible subject losses due to the potential exclusion of subjects 1) enrolled after the abdominal CT scan results are known or 2) lost to follow-up. Our estimate for the total accrual period is 36 months. Once we reach our target sample size with regards to the outcome of interest (IAI, n=877), we will stop enrollment for the derivation of the decision rule.

6 Site Monitoring

Site monitoring visits will be performed by staff from the data coordinating center, to ensure that all regulatory requirements are being met and to monitor the quality of the data collected. During site monitoring visits by the data coordinating center, MCHB, or CDC staff, patient forms and original source documents will also be inspected. The primary criterion for data element verification is identification in the source document, which is either the data collection form or the medical record. The site monitor will assess and verify adequate patient accrual, especially with regard to how many eligible patients were missed (described in Section 4.1 on page 10).

7 Human Subjects

7.1 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 form. 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 abdominal CT scan use in the future. Radiation exposure to future injured children will be reduced and lives will be spared from radiation-induced malignancies, and missed injuries will be potentially decreased as abdominal CT scans are obtained appropriately in high-risk children.

7.1.1 Protection Against Risks

Patient names and addresses will not be sent to the data coordinating center at the University of Utah. To prepare the analytical database, the data coordinating center will encrypt patient and institution identifiers so that the analytical database will be free of patient identifiers, and will be a de-identified data set in accordance with definitions of the Health Insurance Portability and Accountability Act (HIPAA). This analytical database will be the only one available for the analysis of the current and future derivative studies.

7.1.2 Data Security

The data coordinating center at the University of Utah has a dedicated, locked server room within its offices, and the building has 24 hour on-site security guards. The data coordinating center has a state-of-the-art computer infrastructure and coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the data coordinating center with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. TrialDB is the clinical trials software used at the data coordinating center in Utah, and eRoom^{TM}is used for communications about the study. TrialDB, eRoom^{TM}and other web applications use the SSL protocol to transmit data securely over the Internet.

Direct access to data coordinating center computers is only available while physically located inside the data coordinating center offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

The investigators and staff of the data coordinating center are fully committed to the security and confidentiality of all data collected for PECARN studies. All personnel at the data coordinating center at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with data coordinating center data systems have received Human Subjects Protection and HIPAA education.

7.2   Consent Process

The parents, guardians or responsible family members of all patients eligible for this study will be provided an information sheet (see attached) describing the ongoing study, and the parent, guardian or responsible family members of patients discharged from the ED will be informed that they will be contacted for a brief telephone follow-up survey. Unless the parent, guardian or responsible family member 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.

This is a minimal risk study with no therapeutic interventions. The study's only intervention is a brief follow-up telephone survey of parents or responsible family members of patients discharged home from the ED. Therefore, 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, from the medical record of those children who are hospitalized, and review of the medical records of those children who are lost to follow-up. The second part is the telephone follow-up survey of the parents, guardian or responsible family member of those children discharged home from the ED.

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

7.2.1   Part 1: ED and hospital data gathering phase

The ED and hospitalization data needed for this study are gathered routinely during the evaluation of a child with abdominal trauma, and this is an observational study with no therapeutic intervention. This part of the study (i.e. ED and hospital data gathering) 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 subject's parent, guardian or responsible family members will be provided with study information (at the time of the ED visit).

As described in Section 7.1 on page 16, there is no more than minimal risk to the patient. Protection from these risks is described in Section 7.1.1 on page 17. Waiver of consent will not adversely affect the rights and welfare of the subjects.

It is not possible to carry out this study without the waiver from informed consent. The parent, guardian, or responsible family members 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, $\approx 35\%$ of subjects will be victims of motor vehicle collisions. In the currently ongoing PECARN study "Childhood head trauma study", patients' parents, guardians or responsible family members are not present at the time of ED evaluation in 30% of cases. The parents or guardians 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.

The scientific rigor and generalizability of this minimal-risk, yet very important, observational study would be compromised without the waiver from informed consent. 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. This would introduce case ascertainment bias that could substantially bias the decision rule derived from the study. In addition, the data collection form must be completed prior to knowledge of the abdominal CT scan results if a CT is obtained. Delaying enrollment

until a parent, guardian or responsible family member is available would likely eliminate a large percentage of eligible patients because the results of the abdominal CT scan would be known prior to arrival of the parent, guardian or responsible family member. This would lengthen the period of time needed to recruit the large number of subjects needed to construct the decision rule, and would make it impossible to accomplish the study within three years.

7.2.2 Part 2: Telephone follow-up phase

The second part of this study is the telephone follow-up survey of parents, guardian or responsible family members of children discharged to home from the ED. We are requesting waiver of written informed consent from this aspect of the study as well because it meets the other 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 parent, guardian or responsible family member will be contacted by telephone for follow-up. Unless the parent, guardian or responsible family member refuses, they will be contacted by the PECARN site investigator or trained research assistant 1-2 weeks after ED evaluation. During this brief (3-5 minute) telephone call the following few questions will be asked, and the answers will be recorded onto the data collection form:

- whether the child had to return to a health-care facility for signs or symptoms of IAI
- whether the child was subsequently diagnosed with an IAI by CT
- whether the child required an abdominal surgical procedure for their IAI
- whether the child required hospitalization for their IAI

If the parent, guardian or responsible family member of 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, in order to assure the accuracy of the decision rule derived in the study.

The follow-up phase of this study meets criteria for waiver under the following Federal regulations:

- 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."

- 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, guardian or responsible family members. We will not be contacting the child.

7.3 Record Retention

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

7.4 Health Insurance Portability and Accountability Act

Registration of research subjects in the TrialDB system used by the CDMCC at the University of Utah requires a date of birth, race, ethnicity, and gender. These demographic data are held in database tables that are separate from coded research data (including clinical data). The demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

Additional potential identifier information includes the date of admission. Prior to statistical analyses, dates will be used to calculate lengths of stay and patient age. The final data sets (used for study analyses and

archived at the end of the study) will be de-identified, and will exclude these specific dates.

The data coordinating center produces the de-identified research data sets that will be used for all analyses in this project. Since the raw data includes potential identifiers, such as dates of birth and admission, all sites have been offered a Business Associate Agreement (BAA) with the University of Utah. The BAA explains that the data coordinating center is producing the de-identified data using the data submitted by the site, and the University of Utah assumes responsibility to preserve the confidentiality of the original data. Copies of executed Business Associate Agreements are maintained at the data coordinating center in Utah.

Patient identification at the HEDA site is present on the data forms, in order to enable auditing of data quality, and contact information is recorded in order to accomplish telephone follow-up. These data will not be sent to the data coordinating center, but will be retained in locked filing cabinets in locked offices in the HEDA itself. These records should be retained until the study data have been completely cleaned, data lock has occurred, and all primary and secondary publications have been completed. In accordance with Section 7.3 on the previous page, these records will be retained for at least 3 years after completion of the research. At that time, all records with identifying information will be destroyed.

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