

Statistical Analysis Plan

Protocol Title (Number): Development and Testing of a Pediatric Cervical Spine Injury Risk Assessment Tool (C-SPINE) (PECARN 042)

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Abbreviations

Abbreviation	Definition
DCC	Data Coordinating Center
CRF	Case Report Form
SAP	Statistical Analysis Plan
CSI	Cervical Spine Injury
ACTA	Applied Cognitive Task Analysis
CART	Classification and Regression Trees
PECARN	Pediatric Emergency Care Applied Research Network
ED	Emergency Department

1 PREFACE

1.1 Purpose of SAP

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the protocol: Development and Testing of a Pediatric Cervical Spine Injury Risk Assessment Tool (C-SPINE).

The structure and content of this SAP provides sufficient detail to meet the requirements and standards set by the Data Coordinating Center (DCC).

1.2 Auxiliary/Other Documents

The following documents were reviewed in preparation of this SAP:

- Protocol: Development and Testing of a Pediatric Cervical Spine Injury Risk Assessment Tool (C-SPINE).
- Case Report Forms (CRFs) for the C-SPINE protocol

The reader of this SAP is encouraged to read the protocol for details on the conduct of this study, and the operational aspects of clinical assessments.

The purpose of this SAP is to outline the planned analyses to be completed for the C-SPINE trial. The planned analyses identified in this SAP will be included in future study abstracts and manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed. Any post hoc, or unplanned, analyses not explicitly identified in this SAP will be clearly identified as such in any published reports from this study.

It is possible that, due to updates or identification of errors in specific statistical software discussed in this SAP, the exact technical specifications for carrying out a given analysis may be modified. This is considered acceptable as long as the original, prespecified statistical analytic approach is completely followed in the revised technical specifications.

2 STUDY OBJECTIVES AND OUTCOMES

2.1 Study Objectives

2.1.1 Primary Objective(s)

The primary objectives of the C-SPINE trial are:

1. Develop the Pediatric Cervical Spine Injury (CSI) Risk Assessment Tool in children with blunt trauma using prospective observational data obtained from ED providers.
2. Validate the Pediatric CSI Risk Assessment Tool in a separate population of children with blunt trauma using prospective observational data obtained from ED providers.
3. Validate the Pediatric CSI Risk Assessment Tool in a population of children with blunt trauma using prospective observational data obtained from EMS providers.

The tool will have high sensitivity (lower 95% confidence limit > 95%) and adequate specificity (lower 95% confidence limit > 40%) in both the derivation and validation sets.

2.1.2 Secondary Objective(s)

None

2.2 Study Outcomes

2.2.1 Primary Outcome(s)

The primary outcome is CSI which is defined as: vertebral fracture, ligamentous injury, intraspinal hemorrhage, or spinal cord injury (on either MRI or spinal cord injury without radiographic association) involving the cervical region of the spine (occiput to the 7th cervical vertebra including ligamentous structures attaching the 7th vertebra to the 1st thoracic vertebra). The presence of CSI will be determined by review of study site cervical spine imaging reports and, if applicable, spine surgeon consultation notes and phone follow-up.

2.2.2 Secondary Outcome(s)

None

2.2.3 Tertiary Outcome(s)

None

2.2.4 Safety Outcome(s)

None

3 STUDY DESIGN AND METHODS

3.1 Overall Study Design

C-SPINE is a prospective observational study for developing a clinical decision rule for CSI in children after blunt trauma. The study will occur in two phases: development and validation. Data from the development cohort will be used to construct a useable clinical decision support tool. The performance characteristics of the tool will be determined in the independent validation cohort as well as the cohort of all EMS provider observations.

3.2 Method of Treatment Assignment and Randomization

No intervention is being implemented in this study, thus there will be no randomization of participants.

4 STUDY SUBJECTS AND ANALYSIS POPULATIONS

4.1 Eligibility

participants will be eligible for enrollment if they meet the following inclusion criteria:

1. Age 0-17 years; AND
2. Known or suspected exposure to blunt trauma regardless of whether or not injuries were sustained; AND
3. One of the following:
 - (a) Undergoing trauma team evaluation; OR
 - (b) Transported from the scene to site facility by EMS; OR
 - (c) Undergoing cervical spine imaging at site facility; OR
 - (d) Transferred to the site facility with cervical spine imaging.

Participants will be excluded if they are exposed to solely penetrating trauma mechanism (example: gunshot or stab wound).

4.2 Populations for Analyses

4.2.1 Screening Population

The Screening Population consists of all participants who met inclusion criteria (even if they were excluded). This population is used for the CONSORT diagram, demographics summaries, and enrollment summaries.

4.2.2 ED Provider Rule Development Population

The ED Provider Rule Development Population (EDDev) includes all participants enrolled into the study during the development phase. The EDDev population will be used to develop the decision rule (Primary Objective 1).

4.2.3 ED Provider Rule Validation Population

The ED Provider Rule Validation Population (EDVal) includes all participants enrolled into the study during the validation phase. The EDVal population will be used to validate the decision rule (Primary Objective 2).

4.2.4 EMS Provider Rule Validation Population

The EMS Provider Rule Validation Population (EMSVal) includes all participants enrolled during either phase of the study for whom data were collected from EMS providers. The EMSVal population will be used to validate the decision rule for EMS providers (Primary Objective 3).

5 GENERAL ISSUES FOR STATISTICAL ANALYSES

5.1 Analysis Software

Analysis will be performed using both Minitab® v 20.2 and SAS® Software version 9.4 or later whenever possible. Other software packages, including R and StatXact®, may be used for particular specialized procedures.

5.2 Methods for Withdrawals, Missing Data, and Outliers

This study is operating under a waiver of informed consent and few participant withdrawals are expected. However, in the case that a participant or participant's legal guardian requests that the child's data not be included, that participant's data will be removed from the data base and will not be included in any analysis.

Outliers will be reviewed for validity. Outliers that are valid will be included in all analyses and reports for this study.

We will review missingness for all candidate predictor variables over the course of the study using interim reports [Section 6](#). Missing values will be defined as unexpected null values or responses of "Did not assess". Expected null values are those for which the answer to a lead-in question (typically "No") precluded a response. These expected null values will be recoded to logically align with the answer to the lead-in question. Specific methods for handling missing data for each analysis approach are described in [Section 7.2](#).

5.3 Multiple Comparisons and Multiplicity

No analyses are planned that will require an adjustment for multiple comparisons.

5.4 Planned Subgroups, Interactions, and Covariates

The CSI risk assessment tool will be designed and validated using all children who present to the ED with blunt trauma. However, the operating characteristics of the tool will be assessed on the following key and high-risk sub-samples of children:

- Children without cervical spine imaging prior to presentation,
- Children who do not have trauma team activation,
- Children who arrive via EMS,

- Children who arrive via private motor vehicle,
- Young children (< 8 years),
- Children with injuries that require either surgical stabilization or stabilization with an orthotic device for > 30 days,
- Children with medical conditions that predispose to CSIs,
- Children who are victims of abusive trauma.

For any subgroup with poor tool performance (lower confidence limit for sensitivity $< 95\%$ or for specificity $< 40\%$), a separate rule will be derived as an exploratory analysis.

5.5 Derived and Computed Variables

Algorithms for all derived and computed variables will be detailed in the Analysis Dataset Specifications document which will be created for this study.

5.6 Quality control of Statistical Programming

All statistical programs for the derivation of variables and reporting of trial results will be independently verified through dual programming or code review. Two statisticians will each program all datasets for the study and programs for the results will be code reviewed. This process will begin after the Analysis Dataset Specifications are created and will continue through writing of abstracts and manuscripts.

6 INTERIM ANALYSES

6.1 Frequency of and Timepoints for Interim Analysis

This study has two types of planned interim analysis. First, reports will be created to assess rates of missing data for both the ED and EMS providers during the collection of data from both the derivation and validation cohorts. Second, the operating characteristics of the risk assessment tool will be calculated during study enrollment.

Missingness Reports Reports summarizing the rate of missing data for each data element by site and overall will be created and updated regularly. These reports will be reviewed at least monthly throughout enrollment to identify areas of concern.

7 PLANNED ANALYSES

7.1 Description of Subject Characteristics

Publication of the primary results will include reporting of key baseline characteristics overall and for the derivation and validation cohorts. These will include, but are not limited to

- age
- gender
- race
- ethnicity
- injury mechanism

7.2 Primary Outcome Analysis

The primary outcome of this study is CSI which is defined as: vertebral fracture, ligamentous injury, intraspinal hemorrhage, or spinal cord injury (on either MRI or spinal cord injury without radiographic association) involving the cervical region of the spine (occiput to the 7th cervical vertebra including ligamentous structures attaching the 7th vertebra to the 1st thoracic vertebra). The presence of CSI will be determined by review of study site cervical spine imaging reports and, if applicable, spine surgeon consultation notes and phone follow-up.

The CSI Risk Assessment Tool will be derived and validated using logistic regression, bivariate analyses, and CART. This will result in a tool that is either a clinical decision tree or a risk calculator. The choice of which approach will ultimately be used will depend on the Applied Cognitive Task Analysis (ACTA) as described in the study protocol. The methods for deriving and validating the tool using either CART or logistic regression are described below.

For either approach, an acceptable tool will have high sensitivity (lower 95% confidence limit > 95%) and adequate specificity (lower 95% confidence limit > 40%) in both the derivation and validation sets.

7.2.1 Candidate Predictor Variables

Candidate predictor variables for both the CART and logistic regression approaches will be limited to data obtained directly from the ED provider survey or derived from these data. Candidate predictors must also have unexpected missingness rates of less than 10%. All

candidate predictor variables will be specified in the analysis dataset specifications that will be created for this study.

7.2.2 CART

CART Settings and Validation We will use Gini splitting rules to generate the CART trees. Cost of incorrectly misclassifying a participant with CSI will be treated as 250-fold higher than cost of incorrectly misclassifying a participant without CSI.

During the model-building phase using the EDDev population, we will internally validate the generated decision rules using 10-fold cross validation. This validation technique is performed by partitioning the data into 10 strata, with each stratum 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.

In addition, we will externally validate the generated decision rules using data from the EDVal and EMSVal populations as described in [Section 4.2](#).

Missing Data In the CART analysis, surrogate splits will be used to classify participants with missing data for candidate predictors. As specified above, any variables missing for 10% or more of participants will not be considered.

8 SAMPLE SIZE DETERMINATION

Sample size for this study is based on the number of participants needed to be able to achieve a sufficiently high sensitivity in the EDDev, EDVal, and EMSVal datasets. Given an expected rate of CSI of 1.8%, approximately 13,333 participants must be enrolled to obtain 240 participants with CSI in the EDDev population. The validation phase will have 2/3 the number of events or 160 participants with CSI. This will require 8,889 participants in the EDVal. It is projected that EMS providers will provide data for 33.5% of participants resulting in 134 CSI events and 7,444 participants in the EMSVal population. The table below summarizes the sensitivity and exact lower confidence bound under different conditions.

Population	Cohort Size	Children with CSI	Sensitivity (lower 95% CB) 2 children misclassified	Sensitivity (lower 95% CB) 1 child misclassified	Sensitivity (lower 95% CB) no children misclassified
EDDev	13,333	240	99.2% (97.0%)	99.6% (97.7%)	100.0% (98.5%)
EDVal	8,889	160	98.6% (95.6%)	99.4% (96.6%)	100.0% (97.7%)
EMSVal	7,444	134	98.5% (94.7%)	99.3% (95.9%)	100.0% (97.3%)

References

- [1] Wan Y, Datta S, Conklin DJ, Kong M. Variable selection models based on multiple imputation with an application for predicting median effective dose and maximum effect. *emJournal of statistical computation and simulation*. 2015;85(9):1902-1916. doi:10.1080/00949655.2014.907801.