Coversheet

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PI name: Monica Vavilala

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PEGASUS-Argentina

Implementation Fidelity and Benefits of the Critical Care Pediatric Guideline Adherence and Outcomes Program in Traumatic Brain Injury-Argentina

MPIs: Monica S Vavilala, MD and Michael J Bell, MD

UW IRB# STUDY00005629

Clinicaltrials.gov NCT 03896789

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01/01/2019 to 12/31/2023

Table of Contents

Chapter 1. STUDY OVERVIEW

Globally, over three million children sustain a traumatic brain injury (TBI) each year, with an estimated 3-7% being classified as having a severe TBI (Glasgow Coma Scale (GCS) score ≤8). Long-term TBI-related disability and high health care costs are a significant burden to individuals and society, although data are limited outside of the United States and Europe.[1,2] The Brain Trauma Foundation (BTF) Guidelines for Management of Pediatric Severe TBI represent the most comprehensive synthesis of evidence-based care for children with severe TBI,[3] but they are not systematically implemented[4] and are also almost exclusively based on evidence from research in the United States and Europe.

Pediatric Guideline Adherence and Outcomes (PEGASUS) Argentina is a National Institutes of Health (NIH)-funded, multi-site randomized controlled trial (RCT) currently testing implementation of best practice care for children with severe TBI in South America.[5] In prior work, we found that adherence to the TBI guidelines was associated with 6% better outcomes in 5 leading U.S. academic centers. The single center PEGASUS program pilot at Harborview Medical Center (Level-1 pediatric trauma center in Seattle, Washington) demonstrated improved adherence to key performance indicators of the BTF guidelines and patient outcomes, while not increasing in-hospital costs.[6,7] However, TBI guideline adherence remains low, and the guidelines have limitations related to recommendation applicability across health care systems and across countries. While feasible, acceptable, and efficacious in the pilot study, the next step is to test PEGASUS intervention effectiveness more broadly. Focus on our partnership with experienced TBI researchers in Argentina at the Centro de Informática e Investigación Clínica (CIIC), and implementation at South American hospital sites will expand evidence of which guidelines are most important contributors to three-month patient outcomes and examine generalizability of the PEGASUS program.

The study hypothesis is that the PEGASUS program improves TBI guideline adherence during the first 3 days of intensive care in all children severe pediatric TBI and stratified by extracranial injury status. Sixteen hospitals throughout Argentina (14), Chile (1), and Paraguay (1) are participating in this study (Chapter 3.2).

1.1 Specific Aims

1) Determine the relationship between PEGASUS program implementation and TBI guideline adherence (Aim 1a) and assess system, provider, patients, implementation, and guideline factors associated with TBI guideline adherence (Aim 1b).

2) Create a value stream map (VSM) that readily identify value added process of care associated with TBI guideline adherence.

3) Use computer simulation to develop and disseminate a real-world best practices blueprint for TBI guideline adherence.

This is a necessary advance and a step towards implementing guideline-based TBI care for children who suffer from TBI.

**A cost analysis component is also included, although it is not a separate aim.

1.2 Funding

Research is supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award number R01NS106560 (PIs: Vavilala, MS and Bell, MJ). Primary award is to the University of Washington (UW), subcontracts awarded to support CIIC, CNH, and WSU. Study hospitals receive funding through CIIC based on patient enrollment as well as subsidized travel.

The sponsor and funder had no role in the design of this study and will not be involved in the implementation, analyses, interpretation of data, or writing of manuscripts for publication.

1.3 IRB Protocol

The study protocol (UW IRB# STUDY00005629) was initially approved by the UW Institutional Review Board (IRB) on 09/28/2018 as minimal risk. Study design revision was approved on August 7, 2020 and modification assessed as minimal risk. Approval was obtained at the IRBs for each of the local study hospitals for local recruitment, consent, and activities.

Chapter 2. STUDY ORGANIZATION AND RESPONSIBILITIES

2.1 Coordinating Center

The University of Washington is the Coordinating Center. Roles and responsibilities include:

- Development of the randomization scheme and procedures
- Development of intervention plan
- Development of the data flow and data management procedures, including data entry, error identification, and correction
- Development of data collection forms
- Development of value stream mapping app
- Communications with secondary centers, scheduling of meetings, and responding to ad hoc communications
- Quality control procedures
- Statistical analysis
- Subject matter expertise
- Reports (e.g. enrollment, participant status, site performance, quality control, DSMB)
- Distribution of updates, documents, and reports to secondary sites, study sites, DSMB, IRB, FITBIR, NIH, as necessary

2.2 Secondary Centers

Centro de Informática e Investigación Clínica (CIIC) is responsible for:

- Communications with study sites, study IRBs, and coordinating center
- Co-development of intervention, procedures, and forms

- Training of study sites
- Site visits to ensure adherence to protocol and procedures
- Database development and management
- Data entry and cleaning
- Subject matter expertise
- Translation

Children's National Hospital (CNH) provided:

- Subject matter expertise
- Co-development of intervention, procedures, and forms

Washington State University (WSU) provided:

- Cost analysis and utilization

2.3 Study Sites

The study sites (site PI and site coordinators) are responsible for:

- Participation in the protocol finalization and preparation of study materials
- Compliance with protocol and IRB regulations
- Recruitment, screening, and enrollment of participants
- Protection of participants' rights
- Training of pediatric intensive care unit (ICU) staff and intervention implementation
- Data collection and participant follow-up through study completion
- Transfer of data to secondary center (CIIC)
- Communication of questions, concerns, and observations to secondary and coordinating centers.

2.4 Roster

Name	Role	Affiliation	Phone	Email
Dr. Monica Vavilala	Project Director/ Principal Investigator (PI)	University of Washington, Seattle, WA	206-744-9454	vavilala@uw.edu
Dr. Michael Bell	Project Director/Principal Investigator (PI)	Children's National Hospital, Washington, DC	202-476-2037	mbell@childrensnational.org
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Dr. Silvia Lujan	Co-Investigator	Centro de Informática e Investigación Clínica (CIIC), Rosario, Argentina	+54.341.4721030	silviablujan@gmail.com

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Dr. Megan Moore	Co-Investigator, Qualitative	University of Washington, Seattle, WA		mm99@uw.edu
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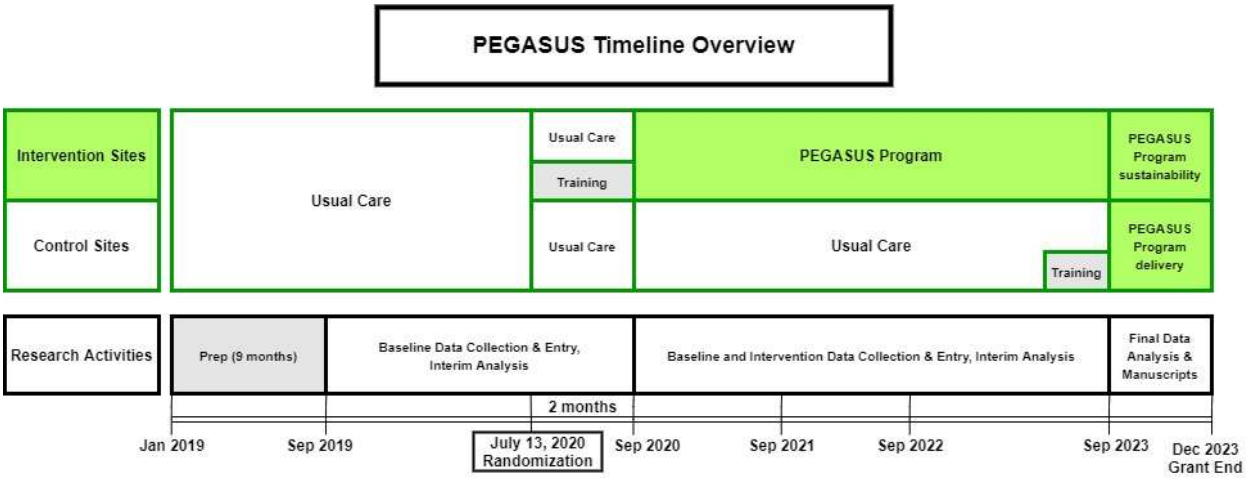
Alejandra DePetris	Translator/Administrative	Centro de Informática e Investigación Clínica (CIIC), Rosario, Argentina		info@ciic.org.ar

CHAPTER 3. STUDY DESIGN

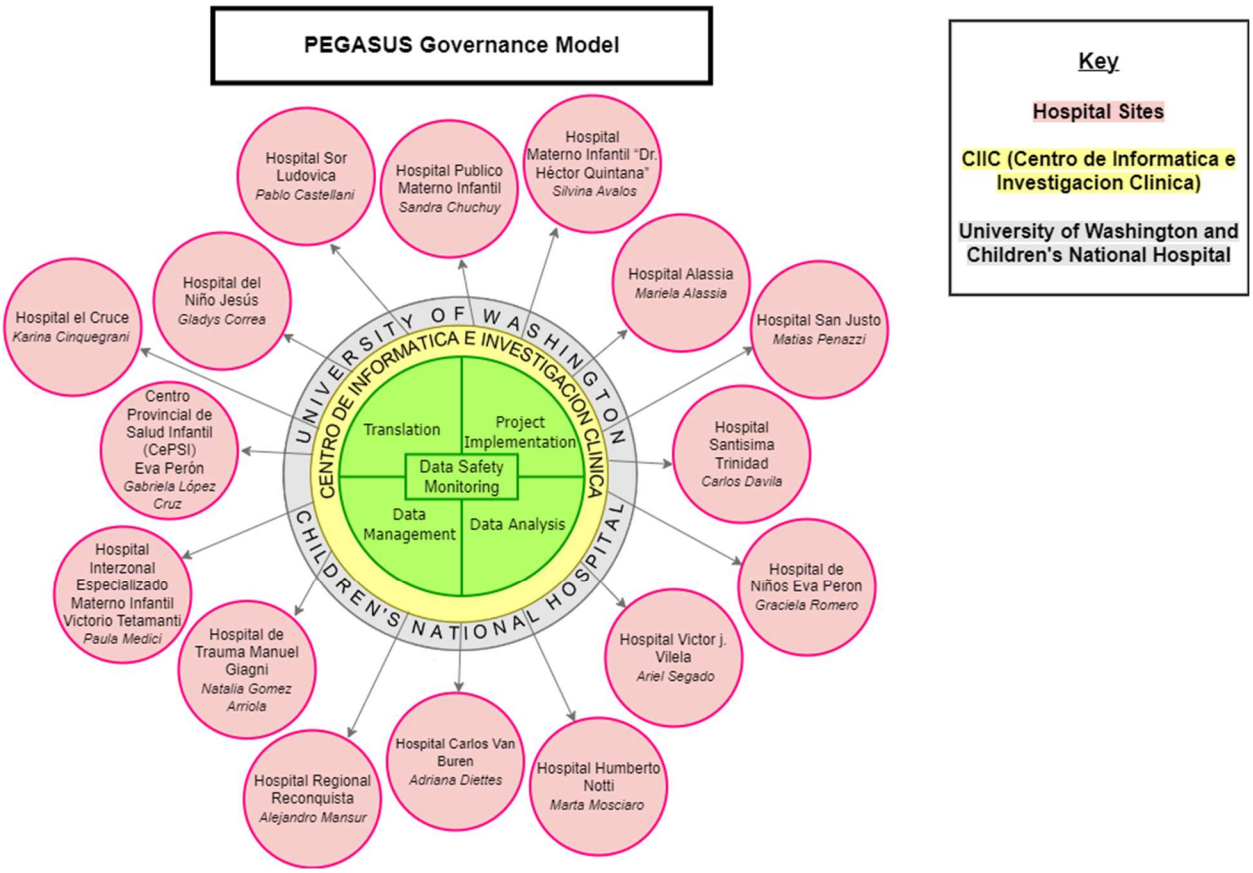
3.1 Study Design

This study is an open-label, multicenter, phase 3, superiority, pragmatic, parallel cluster randomized controlled trial (RCT) including 16 South American hospitals to provide usual care (n=8 sites) or the PEGASUS intervention (n=8 sites). This final design resulted after two iterations: the first iteration was a parallel cluster RCT with twelve sites (6 intervention, 6 control). In response to site requests for receiving the PEGASUS Pathway intervention, a stepped wedge design was developed and approved by the sponsor. However, the final study design was again updated in August 2020 after approvals from site PIs and sponsor from a stepped-wedge design due back to a parallel cluster RCT with sixteen sites (8 intervention, 8 control) due to COVID-19 pandemic challenges.[8]



3.2 Governance Model

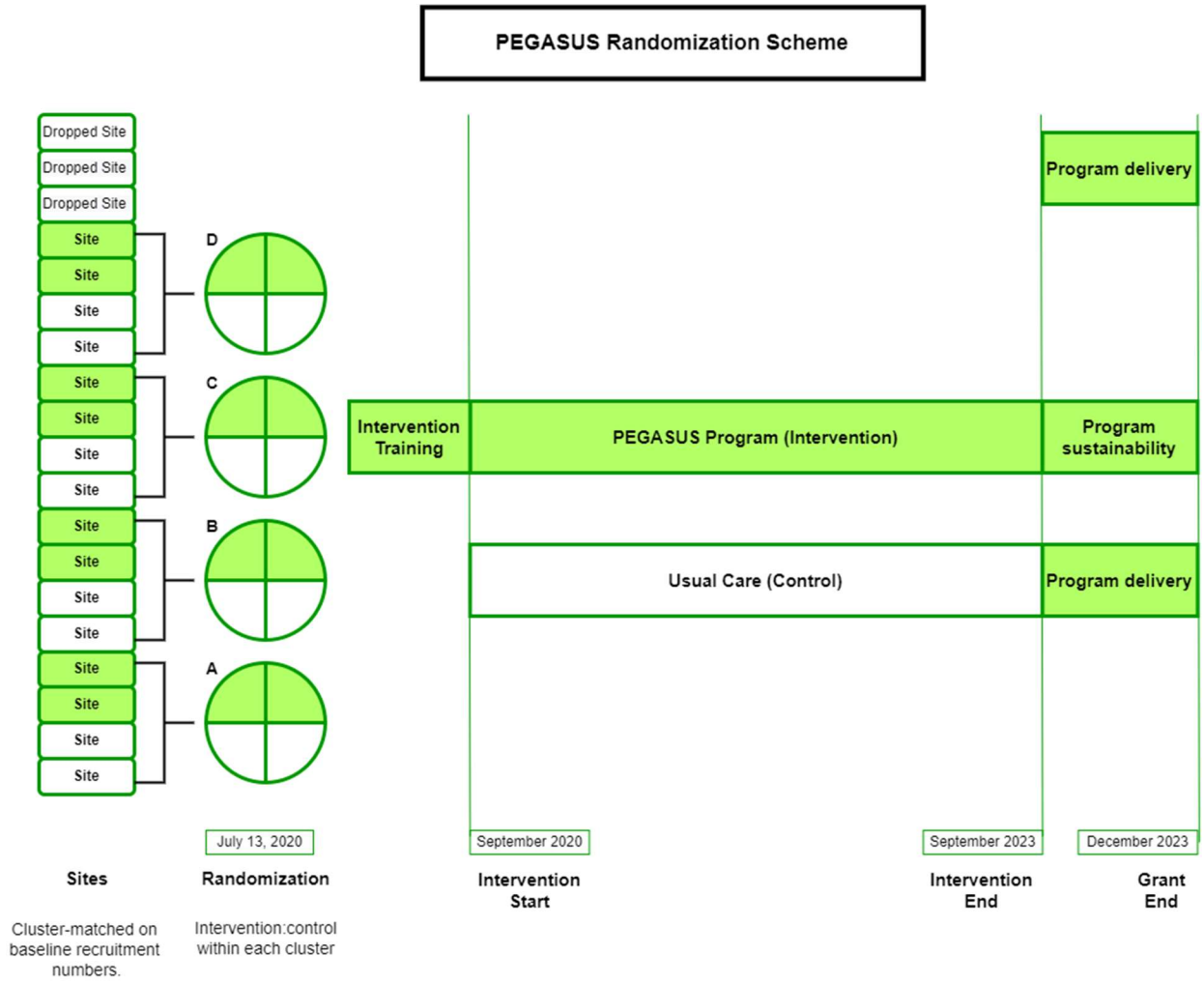
The University of Washington and Children's National Hospital supports CIIC's coordination of the sixteen hospital study sites for translation, project implementation, data management, data analysis, and data safety monitoring components.



3.3 Site Randomization Plan

Sixteen study sites were recruited by CIIC based on willingness to participate and annual severe TBI admissions. Sites were added after the original proposal to increase the potential patient recruitment population. All sites receive compensation for data submission. Prior to randomization on July 13, 2020, three sites who had no or one enrolled patient during ten months of baseline usual care data collection were removed from the pool. The remaining sixteen sites participating were ranked by median monthly baseline enrollment, number of zero recruiting months, and total number of recruited patients and divided into four groups (Group A=highest enrollment group, Group D=lowest enrollment group). The study statistician performed computer block randomization within each group to assign to control and intervention arms at a 1:1 ratio. Participant assignment was dependent on the intervention or control arm assignment of the study hospital to which they were admitted.

Due to the nature of the intervention study team, site staff, and patients' families are aware of the site's arm assignment.



3.4 Screening and Eligibility Criteria

All pediatric patients who admitted to the ICU at a study hospital site with a TBI are screened and their families/guardians are approached to enroll. Patients who are not eligible at admission but deteriorate are included at the time deterioration is assessed. No other exclusions.

To be included the patient must be:

- Age < 18 years
- Mechanism or CT evidence of TBI
- Glasgow Coma Scale (GCS) Score ≤ 8 (if intubated, motor GCS ≤ 5)
- Admitted to ICU at any point in the hospital stay

An enrollment log will be kept in the secure database. Reasons for non-enrollment (does not meet eligibility criteria, death before consent, consent refusal, withdrawal) will be documented.

3.5 Informed Consent

If eligible, the 24-hour-on-call study coordinator is notified to begin a culturally appropriate consent process. Written informed consent for study procedures is obtained from legal guardians of patients by each participating site in Spanish. Verbal assent of the patient is also sought by ICU discharge if the patient is capable. Enrolled participants at the control sites consent to data collection from their medical records. Enrolled participants at the intervention sites consent to data collection and receive the intervention delivered by the trained ICU staff delivering their care. A patient or family/guardians can withdraw consent at any time. Should a patient or their family withdraw their consent, any previously collected data is removed from analysis and, if they are a patient at an intervention site, the PEGASUS clinical pathway is no longer used at the bedside, and they receive needed, usual care. The CIIC served as the regional coordinating center and storage warehouse for documentation. This protocol was performed according to the updated Declaration of Helsinki and all patients provided informed consent per local protocols for trial participation.

3.6 Risks

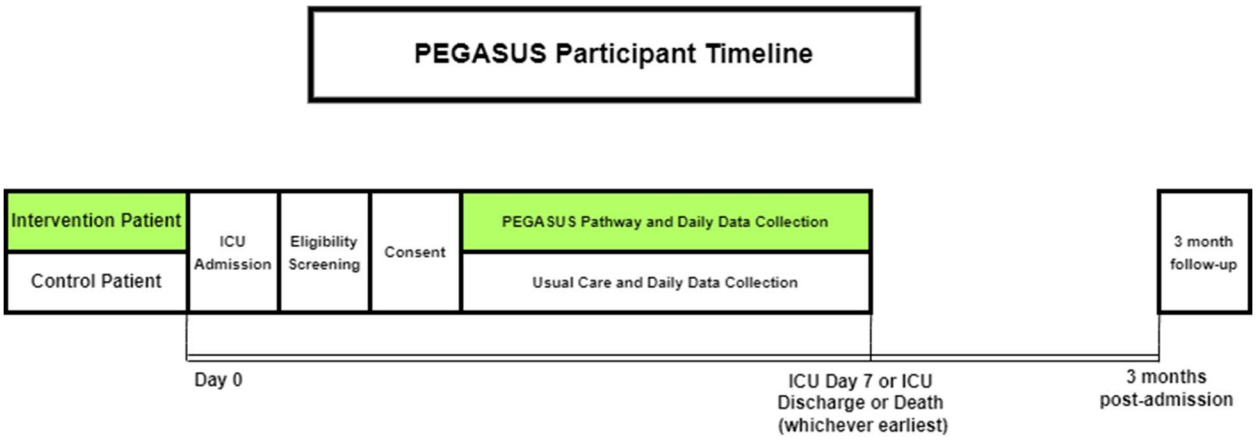
There are minimal risks associated with the proposed study. The main risk for participants is loss of confidentiality, which will be protected as described in Chapter 8. Anticipated and unanticipated health risks will be reviewed and assessed as described in Chapter 5. There are no provisions for post-trial care.

3.7 Sample Size and Power

A sample size of 432 participants is targeted for the planned parallel cluster study, which would have 80% power to detect a 18.7% higher ICU TBI guideline adherence rate with program implementation at the site level, with a two-sided alpha of 5%, and an intraclass coefficient of 0.05. Calculations included 58.6% guideline adherence rate estimate based on prior pilot work in Argentina and assumed no change in adherence rate at control sites. The study will not be sufficiently powered for secondary outcomes of patient mortality, discharge outcomes, or three-month follow-up outcomes.

3.8 Recruitment, Retention & Follow-up

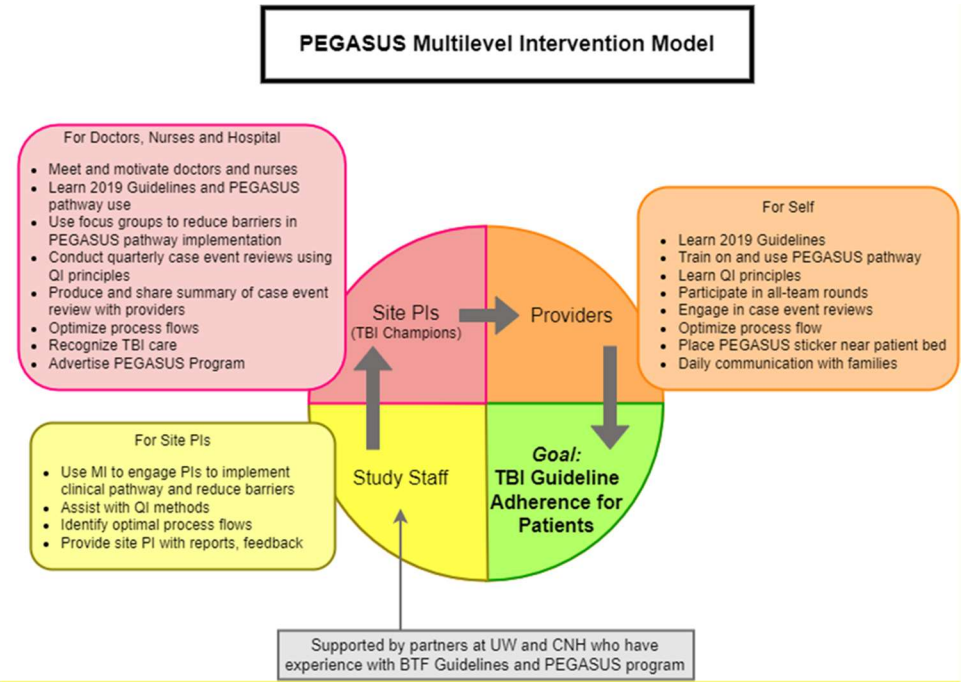
Recruitment is limited to eligible patients admitted and consented at study sites. Based on baseline recruitment levels, the target sample size of 432 is feasible with about 9 participants per site per year. This is an in-patient intervention for the first 7 days of ICU care where intervention ICU staff are trained on intervention delivery as part of their patient care. Other data will be obtained from the health records. Follow-up data collection will be attempted at three months post-admission and can be completed in-person, via telephone, or from the health record. If unable to complete follow-up by four months, the participant will be designated lost-to-follow-up, but in-hospital data will be included. There is no incentive for participation offered to patients at any stage.



CHAPTER 4. INTERVENTION

The PEGASUS program intervention has multi-level components to increase TBI guideline adherence. It will be implemented from October 2020-September 2023. The patient level clinical care pathway is implemented for each eligible, consented patient at an intervention site for up to seven days of their ICU stay. Intervention site care providers supply perspectives and knowledge elements quarterly. At the hospital level, intervention sites participate in quarterly focus groups, morbidity and mortality case reviews and quality improvement efforts, and regular motivational interviewing informed (MI) check-ins with site PIs facilitated by CIIC.

4.1 Intervention Model



4.2 Implementation Readiness

The four overarching program attributes are intent to benefit children with severe TBI (the who), inclusion of evidence-based acute care severe TBI recommendations (the what), program flexibility (the how), and capacity building (the goal). Multilevel refers to outer setting, inner setting, individual, and implementation process. The PEGASUS program meets criteria for innovation domain of the Consolidated Framework for Implementation Research constructs. Actions are given in chronological order. Process times may vary but ranged from 2-3 months. Timeline for process completion may vary depending on local needs.

4.3 TBI Guideline Adaptations

During the baseline study period, the full study team, including the sites provided input on TBI guidelines in the local context and impact on the relevant indicators in the guideline adherence calculation scorecard.

4.4 PEGASUS Pathway

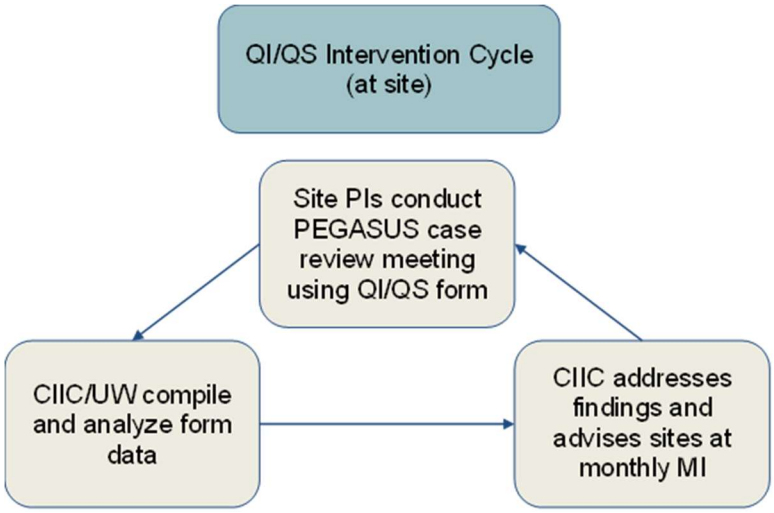
The PEGASUS pathway does not prescribe specific drug doses or treatments but provides guidelines that inform the clinical assessment and treatment for individual patients. The PEGASUS program has been iteratively refined for use in the South American context and includes additional nursing resources for rounding and family education guides to encourage engagement.

As a pragmatic implementation science study with quality improvement efforts, the components of the study are designed to be adaptable to support sites' needs and to evaluate process measures to address reach (number of patients), dose (% processes implemented), and fidelity (variance from recommended

processes and timely clinical pathway adoption). The Theoretical Domain Framework (TDF) and the Determinants of Implementation Behavior Questionnaire (DIBQ) guide these efforts.[9]

4.5 Case Review and Quality Improvement (QI) Intervention Cycle

This QI Cycle is used to support intervention implementation. Intervention sites will select a PEGASUS case to review quarterly with their ICU team. The case review form and follow-up corrective actions will be assessed by the CIIC/UW team.



4.6 Focus Groups and MI Check-Ins

The purpose of the quarterly focus groups and primarily bi-monthly (adaptive) MI check-ins as part of the intervention is to:

- Facilitate engagement in the study
- Promote adherence with PEGASUS protocols
- Address unmet needs while promoting site PI and clinician autonomy

It utilizes adaptable discussion guides based on the TDF and DIBQ domains to maintain engagement to promote changes in the behavior of the site PI and coordinators that translates into improved implementation of the PEGASUS Pathway and the goal of increasing BTF guideline adherence.

CHAPTER 5. SAFETY REPORTING & ADVERSE EVENTS

5.1 Complications Reporting

The UW IRB has determined that the study and the intervention pose minimal risk to participants. However, due to the nature of severe TBI injuries and ICU hospitalization it is anticipated that adverse events and complications, including death, will occur. Site PIs will report to a complications form in the database. The complications form tracks the occurrences, type, and severity (grave, moderate, or mild) of complications that occur. Shock, pneumonia, peritonitis, intraparenchymal hemorrhage, and

arrhythmia are specifically identified, and other complications are noted as free text. We have pre-intervention baseline data to assess adverse events related to patient safety or concerning trends in recruitment or follow-up data and we do not expect higher than baseline adverse events during the implementation of the intervention. If concerned about the impact of the study on an adverse event, site PIs will notify CIIC directly and the concern will be reviewed and escalated.

5.2 DSMB Committee

This study has an internal Data Safety and Monitoring Board (DSMB) comprised of a small group of experts who are not part of the study team. Study PIs, CIIC co-investigators, and the research coordinator will meet with them twice per year to review study status, recruitment, and adverse events, or in the event of an escalation.

The DSMB will review participant recruitment, mortality, surgery type and frequency, and adverse events from the complications form. The study team will categorize complications according to body system. The DSMB will remain blinded to study arms unless a specific, unanticipated concern needs to be address. Reports from the meetings will also be submitted to the UW IRB to comply with IRB requirements.

CHAPTER 6. TRAINING PLAN

The overarching methodology of training for this study is a train-the-trainer model. The University of Washington (MSV) and Children's National Hospital (MJB) trained CIIC (NG, SBL, GP) partners and CIIC investigators trained site PIs in study procedures. Materials were co-developed by the study team. Questions from sites were first fielded in real time and per schedule by CIIC and escalated to MSV and MJB, as deemed necessary by CIIC.

6.1 Data Collection Training

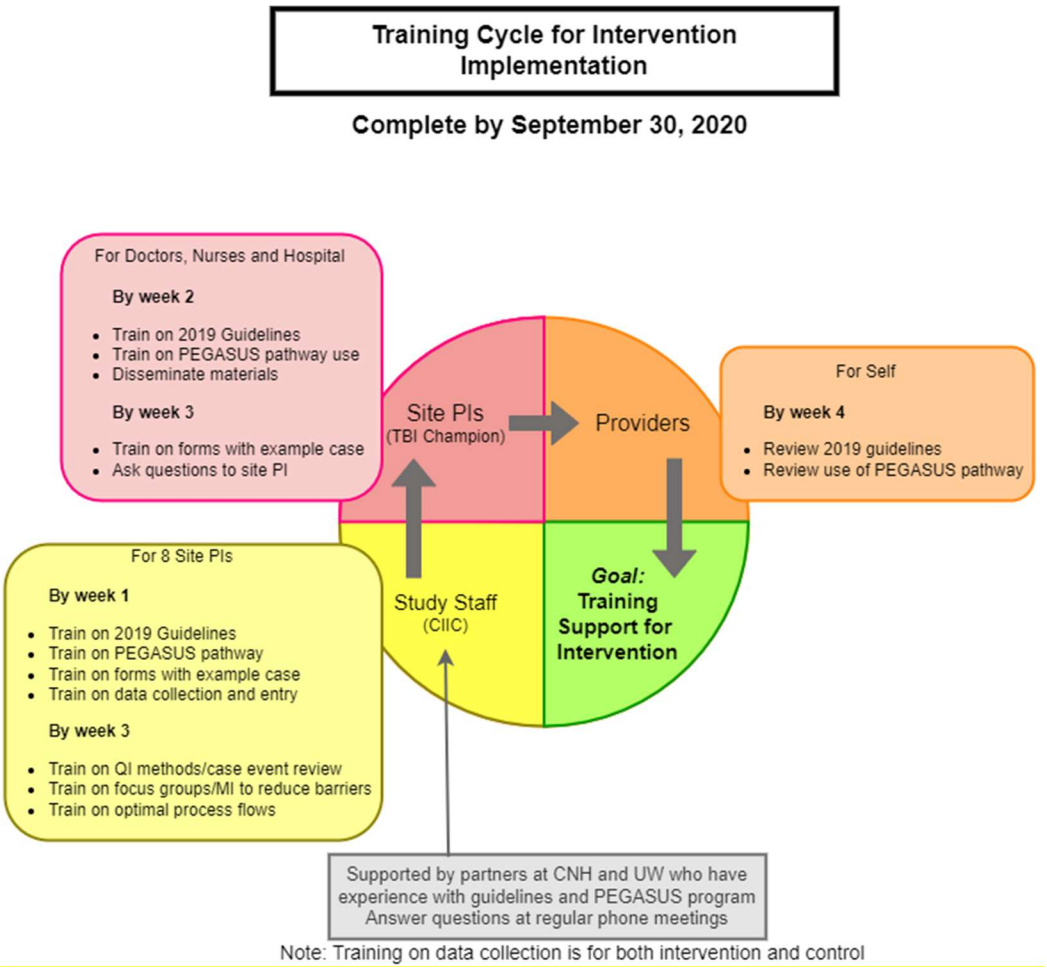
Prior to participant enrollment for baseline data collection, all sites are trained in screening and consenting study participants. Training is conducted in medical record abstraction for patient level usual care data. After introducing the database and data collection forms, sites abstract a medical record from a sample patient as practice. Additional organizational level forms are also reviewed and the first round of these repeated forms are completed. Annually, data collection will be covered during booster trainings and other individual data entry issues will be addressed within the communications with the sites.

UW trains CIIC on concept of process flow and value stream mapping through app demonstration and real-world examples. CIIC trains all site PIs on concepts of process flow and value stream mapping (VSM). Process flows are workshopped by site PIs who provided annual surveys of the ICU workflow.

6.2 Training Cycle for Intervention Implementation

Below is the PEGASUS Training Cycle for Intervention Implementation describing the timing and steps of implementation training for the intervention sites prior to intervention implementation. Annually,

common intervention concerns will be covered during booster trainings and other individual issues will be addressed within the communications with the intervention sites.



Note: Training on data collection is for both intervention and control

6.3 PEGASUS Pathway Training

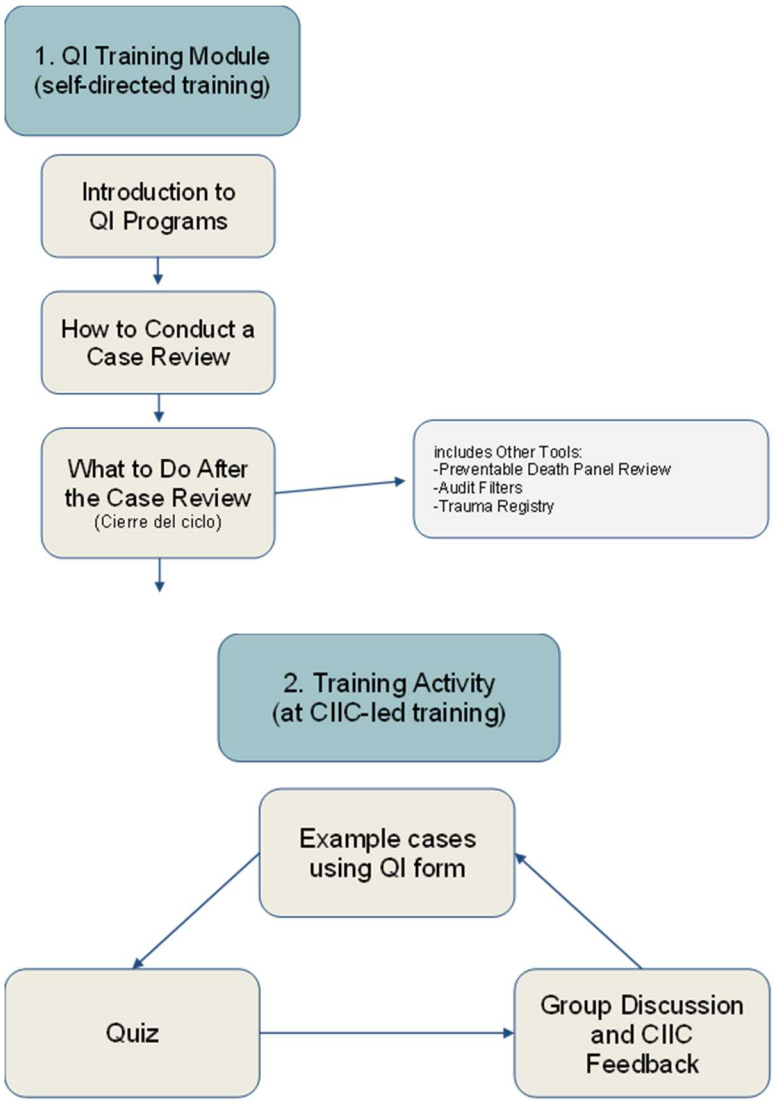
CIIC will lead training with intervention sites prior to implementation to review BTF guidelines and show how they integrate with the PEGASUS Pathway using an example case. Additional nursing resources and rounding tool and a family guide, co-developed by UW and CIIC, will be introduced and provided to support training of ICU nursing staff and for families, respectively.

Intervention sites (site PIs and site coordinators) will then lead training for their ICU staff who care for eligible participants.

6.4 Case Review and Quality Improvement Training Details

The case review training module is adapted from World Health Organization (WHO) trauma quality improvement guidelines by UW with CIIC input. CIIC (SL) attended a Pan-American Health Organization (PAHO)-led training on the topic in 2019. The goal of the case review and QI training is to build capacity at sites for local QI processes. Part One is a case review module consisting of a self-directed training module (recorded presentation) and Part Two, a group case review training activity led by CIIC of three

local cases (deidentified) at the implementation training to be conducted prior to implementation at intervention sites. Annually, QI topics were revisited in booster trainings.



6.5 Focus Group and Motivational Interviewing (MI) Informed Check-In Facilitation Training

Using the train-the-trainer model, UW provides initial facilitation trainings (two sessions) to CIIC on the use of motivational interviewing methods for the regular check-in communication at intervention sites and for focus groups with site PIs, coordinators, and ICU staff. The study team provides support on facilitation to CIIC as needed.

The primary components of this training include:

- Principles of MI
- Basic Principles of a Person-Centered Approach to Behavior Change
- The Flow of MI
- Reveal Discrepancies and Respond to Resistance

- Strengthen Commitment and Make a Change Plan
- Review and Role Play of the Focus Group and Check-In Discussion Guides

CHAPTER 7. COMMUNICATIONS PLAN

UW communicates internally and with CIIC at least weekly. Study PIs and CIIC meet biweekly, and the PEGASUS Argentina study team meets monthly. Meeting minutes will be maintained. Other sub-meetings and ad hoc communications for specific tasks facilitate activities in-between regular meetings. All-team meetings with PIs, study team, CIIC, and site PIs and coordinators (separated by study arm) are annual, via Zoom or in-person, as feasible.

CIIC conducts day-to-day management of intervention delivery and implementation of activities, data entry support, training of study site staff, and direct weekly communication with study sites. Site communication and monitoring is conducted by CIIC to educate, support, and solve problems with data collection, intervention implementation, and quality improvement, with additional input from study PIs and co-investigators as necessary. In-person site visits are conducted as feasible due to travelling restrictions.

CHAPTER 8. DATA COLLECTION, MANAGEMENT, & ANALYSIS

8.1 Data Management

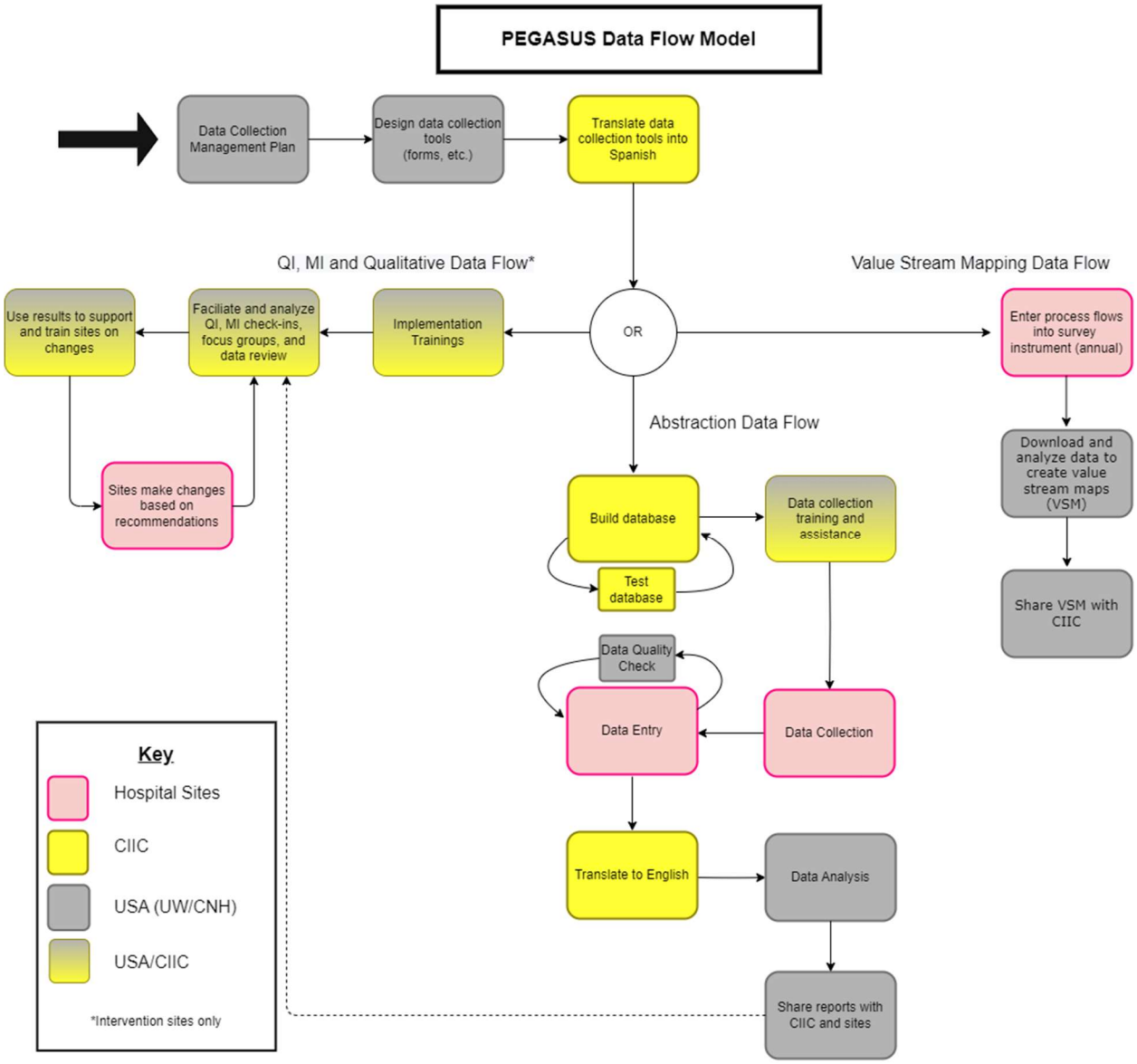
The purpose-built, password-protected database is maintained on a dedicated server and has logic coding and input parameters to ensure legal variable values. Qualitative data for the provider- and hospital-level intervention support include free text response in questionnaires and case reviews, notes, and summaries of focus groups and MI check-ins. Data completion is assessed monthly by UW and CIIC study staff.

8.2 Data Confidentiality

Participant identification codes are assigned at the sites at the time of screening. Hospital site PIs and study coordinators have access to personal identifiers of their site's enrolled patients and medical records through their dual roles as researchers and care providers. CIIC and U.S.-based study staff have access to the full dataset through the PEGASUS database, but without protected personal information like names, birth dates, or contact information.

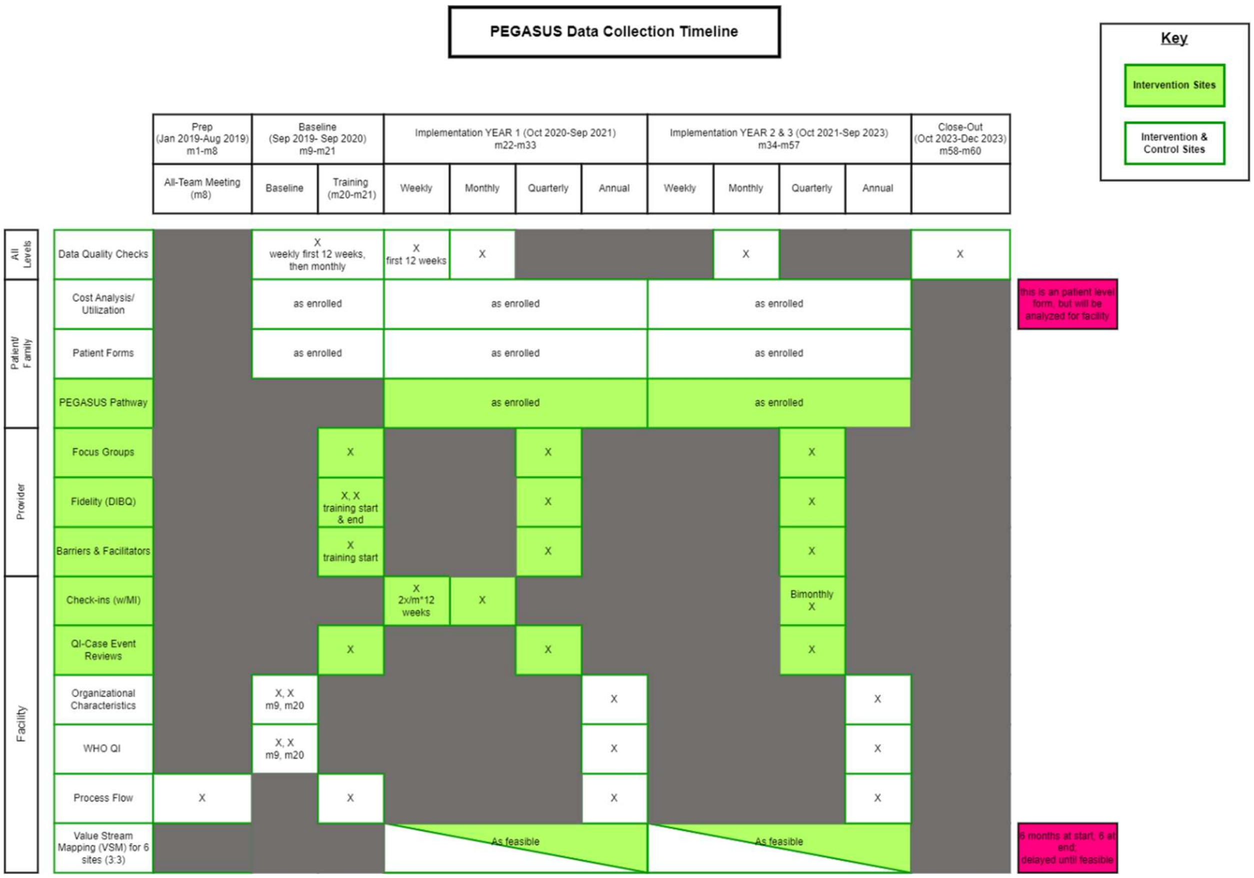
8.3 Data Flow Model

The Data Flow Model below shows the procedures and responsibilities for data collection, data checks, and analysis.



8.4 Data Collection Timeline

Baseline data collection will occur at all participating sites from September 2019-September 2020. From October 2020-September 2023, interventions sites will collect additional data associated with the intervention implementation. The Data Collection Timeline below shows the data types collected (leftmost column) and the intervals of repeated measures.



8.5 Missing Data

Missing data identified during data checks will be followed-up and resolved with site PIs. Participants with missing data will be included in relevant analyses unless they specifically withdraw from the study.

CHAPTER 9 STUDY COMPLETION AND CLOSEOUT PROCEDURES

9.1 Study End

After the study intervention and data collection periods are completed, the study team will share results with all site PIs and engage them throughout the analysis and manuscript writing process and provide sites who participated in the control arm with a training and materials package aimed to facilitate implementation should they desire.

9.2 Dissemination Policy

Access to a cleaned, deidentified dataset and code may be requested after the study is completed and accompanying manuscripts are published. As required by NIH, data will be submitted to FITBIR. The primary aim is a study-wide analysis and will be disseminated as such. We do not expect to have sufficient data for publication at the level of individual sites. Any publications and presentations prior to the release of the primary results will not impede the integrity of those results.

APPENDIX 1: REFERENCES

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APPENDIX 2: ABBREVIATIONS

AIS-Abbreviated Injury Score

BTF-Brain Trauma Foundation

CIIC-Centro de Informática e Investigación Clínica

CNH-Children's National Hospital

DIBQ-Determinants of Implementation Behavior Questionnaire

DSMB-Data and Safety Monitoring Board

FITBIR-Federal Interagency Traumatic Brain Injury Research

GCS-Glasgow Coma Scale

GOS-Glasgow Outcome Scale

GOSE-Peds-Glasgow Outcome Scale Extended Pediatric

ICU-Pediatric Intensive Care Unit

IRB-Institutional Review Board

ISS-Injury Severity Score

ITT-Intent-To-Treat

MI-Motivational Interview

MPI-Multiple Principal Investigator

NIH-National Institutes of Health

NINDS-National Institute of Neurological Disorders and Stroke

PAHO-Pan-American Health Organization

PEGASUS-Pediatric Guideline Adherence and Outcomes

PI-Principal Investigator

RCT-Randomized Controlled Trial

TBI-Traumatic Brain Injury

TDF-Theoretical Domain Framework

UW-University of Washington

VSM-Value Stream Map

WHO-World Health Organization

WSU-Washington State University