PROPLIS Clinical Monitoring Plan

PROPOLIS
PLASMA RESUSCITATION
WITHOUT LUNG INJURY

1. Brief description of study

In this study, we propose to use pathogen-reduced plasma (PRP), an FDA-approved blood component, as part of the resuscitation plan in the initial 24 hours of burn treatment. Adult patients admitted to (and enrollable at) a burn center within 8 hours of sustaining a burn injury > 20% total body surface area (TBSA) and undergoing intravenous fluid resuscitation for at least 24 hours, will be enrolled and randomized. This study will enroll 94 subjects (47 per group) at 6 participating centers (approximately 16 subjects per site) over 2 years. This is an open-label, prospective, randomized, controlled, clinical trial. The control group will receive standard crystalloid resuscitation, while the treatment group will receive 1 mL/kg/%burn of pathogen-reduced plasma over 24 hours in addition to crystalloid. The primary endpoint will be the total volume of all resuscitation fluids delivered between hours 0-24 postburn, in ml/kg.

2. Study hypothesis/objectives

Hypotheses: Administration of plasma for resuscitation after burn injury will 1) reduce 24-hour and 48-hour resuscitation volumes and 2) reduce the incidence of acute respiratory distress syndrome, multi-organ failure and other resuscitation-related morbidities.

Objectives:

- Specific aim 1: To determine whether administration of Pathogen-Reduced Plasma during burn resuscitation results in decreased total resuscitation volumes compared to standard-of-care crystalloid-based resuscitation.

- Specific Aim 2: To determine whether Pathogen-Reduced Plasma administration during burn resuscitation reduces ARDS.

- Specific Aim 3: To determine the effect of Pathogen-Reduced Plasma administration on endotheliopathy, inflammation and coagulation following burns.

3. Description of Monitoring Approaches

The PROPOLIS Clinical Monitoring Plan uses a risk-based approach whereby those activities judged to be of high risk to either the patient or the conduct of the study have comprehensive mitigation strategies and appropriate monitoring methods. Activities that are low risk may have mitigation strategies but not necessarily monitoring methods.

Monitoring activities for PROPOLIS will be conducted as central monitoring and on-site monitoring. Many of the monitoring activities can be conducted online/electronically either through the REDCap database system or through shared file systems whereby remote monitoring of site documents can be conducted. On-site monitoring will be performed for a) activities that are determined to be high risk and are not amenable to remote monitoring strategies; and b) sites that are having difficulty conducting the study or quality issues AFTER remote/virtual monitoring techniques.

4. Critical data and study procedures

The items below are considered to be critical data and study procedures that will be covered in the Clinical Monitoring Plan.

a. Informed consent
b. Adherence to protocol eligibility criteria
c. Procedures for documenting appropriate accountability and administration of the investigational product
d. Conduct and documentation of procedures and assessments related to
    i. Study endpoints
    ii. Protocol required safety assessments
    iii. Evaluating, documenting, and reporting serious adverse events and unanticipated adverse device effects, subject deaths, and withdrawals
    iv. Conduct and documentation of procedures essential to trial integrity

5. Specific risks to be addressed by monitoring

Participant level risks identified		
Risk	**Risk Management Strategy**	**Monitoring**
Potential issues with consent process include multiple languages, consent/enrollment timeline of 8 hours from burn injury, eConsent process	Consent process: • Consents will only by obtained by designated trial-specific personnel • Consent forms translated into appropriate languages for each center • Native language speakers or interpreters to be used when needed • eConsent process approved by WIRB • REDCap eConsent process training provided via web	Central/electronic monitoring • All eConsent forms will be reviewed in REDCap • Hard copy consents will be uploaded to REDCap database for review • Delegation logs will be checked to confirm only delegated personnel obtain consent • Time consent signed will be compared to time plasma begun to ensure only consented patients receive the intervention product

	• Inclusion/exclusion infographic and training to all Burn Center personnel to support enrollment of all eligible patients.	
Confidentiality	• Secure web-based database will be used for a limited data set • Only key study personnel at each site will have access to identifiable patient logs. Logs to be stored in control access location <u>Confidentiality</u> of sensitive data will be maintained according to four general considerations: (1) physical security of servers and the data stores; (2) security of the data while in transit between sites; (3) proper authentication of all personnel with access to the data, and (4) protection of the data from accidental deletion or corruption. Our approach addresses all four of these factors. Our database and web servers are fully firewalled and secured virtual machines running within an institutionally-managed VM environment. All associated physical equipment is collocated in a 24/7 locked data center with rigid cardkey-based access controls. All physical storage media are fully encrypted at rest by way of self-encrypting solid-state hard disks. The	Central/electronic monitoring • The PROPOLIS data center will review user accounts on a regular basis and ensure with the PI of each site that the appropriate staff have access/that no accounts need to be terminated. • The data center will ensure security of servers on an ongoing basis • For hard copies of data, each site PI will ensure that only those people who need to have access are able to review and access data

	logical network traffic is forbidden to transfer beyond the confines of the subnet containing the database server except with specific domain-based authorization on a per-machine and per-user level. Data from PROPOLIS study centers and the laboratory testing centers will be entered directly into the web-based REDCap database developed specifically for this project and will not be stored on local machines or at any "middle-man." All browser transmissions including all data and user credentials are transmitted via HTTPS encryption, similar to technologies used by e-Commerce sites. For circumstances where web-based data transfer is not possible or ideal, our organization provides a variety of other technologies for secure transfer of data files, including Secure File Transfer Protocol, signed and encrypted email technologies, or encrypted physical devices.	
Trial level risks identified		
Risk	**Risk Management Strategy**	**Monitoring**
Potential protocol violations/adherence	• Protocol diagrams/visuals at every bedside of enrolled subjects	• Track training logs

	• Protocol training videos/documents posted on study website • Physician and research coordinator training attendance every 6 months throughout enrollment period of the study	
Potential recruitment issues: • Identification of potential eligible subjects • Timeframe from enrollment • LAR consent • Physical unavailability of LAR	• Each center will ensure robust enrollment plan to identify all eligible subjects in time to consent • CNTR will prepare and distribute an infographic of inclusion/exclusion for use in the clinical area • Each center will use a telephone consent/eConsent process to obtain LAR consent as needed	Central Monitoring- • The number of subjects screened and enrolled will be reported by each center quarterly. • For centers with screen to enrollment below 50%– the center PI will meet with the Steering Committee to discuss the enrollment issues and present a plan to increase enrollment. • LAR consent/eConsents will be reviewed centrally as above
Pharmacovigilance/Safety	• The protocol includes guidelines on SAE, AE, and UP reporting. • Study related AEs will be recorded in the eCRF • All SAEs will be recorded in the eCRF	Central Monitoring • In REDCap, when data triggers notice of an SAE in the eCRF, an automatic email will be sent to the DCC for review
Plasma distribution and management	• The MOP will identify distribution centers supporting the study • A Plasma Management Policy & Procedures document will contain all details with plasma distribution, maintenance of levels, labelling,	• Central Monitoring Track plasma training • REDCap tracking of product par levels, usage per subjects, and re-orders to ensure product is being utilized for treatment pateints.

	storage, dispensing, tracking, and reporting. • Cerus staff will interface directly with Blood Bank/Transfusion Services at each center to develop plan and ensure proper handling of plasma • Cerus will provide plasma training to all centers. The training will be available on the study webpage	
Data Collection and management system	• Internal validity checks • eCRFs • Manual of Procedures provided to each site and available on study webpage • Data dictionary provided to each site and available on study webpage • Data collection training will be provided, and training video will be available on study webpage	Central Monitoring • Track training logs • REDcap programmed such that out of range values cannot be entered
Unreliable outcomes assessments of primary and main secondary outcomes Critical data elements: • Total volume of resuscitation in 24 hrs • Total volume of resuscitation 0-48 hrs • TBSA • Norepinephrine equivalents 0-48 hrs	• eCRFs • Data dictionary provided to each site and available on study webpage • Data collection training will be provided, and training video will be available on study webpage • Manual of Procedures provided to each site and available on study webpage	Central Monitoring- • Comparison of 100% of uploaded CRFs to the database for the critical data elements list • Track study staff data collection training • Repeat data collection training every 6 months

• Serum lactate levels 0-48 hrs • Rescue procedures (CRT, TPE, ascorbic acid, albumin) 0-48 hrs • ARDS • Mechanical ventilation duration • Ventilator free days • SOFA Score • LOS ICU • LOS Hospital • PROMIS Global assessment • TRALI • VTE	• For data elements that are scores, the individual raw components of the score will be in the eCRF/database with the calculation being conducted by the DCC/centrally/automated • If a center uses paper CRF, it will be uploaded as an attachment to the REDCap database for use in monitoring process	
Research laboratory specimen handling and shipping	• Specimen collection and shipping training will be provided and continually available on the study webpage • Specimen collection and shipping procedure document will be distributed to all sites • Infographic depicting specimen collection and shipping procedure will be distributed to all sites	Central Monitoring • Track training logs • Central laboratory will review 100% of specimens received at central laboratory site for compliance with procedure • Central laboratory will report any specimens deemed to be mis-handled/shipped to the PI, Coordinating Investigator, and CTNR within 24 hours of receipt of sample
Staff training issue due to small number of subjects per site over 2 years	• All staff trainings will be continuously available on the study webpage • Quality issues will be communicated to study staff within 48 hours of identification • Study trainings will be reviewed every six months for the	Central Monitoring • Track training logs

	duration of enrollment	

6. Roles/Responsibilities

Role	Responsibiities
Data Coordinating Center	Participate/assist in central monitoring activities Audit data for accuracy Provide reports to the DSMB Develop and manage database
CNTR Program Manager	Participate in clinical monitoring activities Conduct site visits as necessary Manage study webpage Manage updates to Manual of Procedures and Clinical Monitoring Plan
Steering Committee	Ensure compliance with the protocol Participate in monitoring activities
Research Medical Monitor	Review reports of unanticipated problems involving risk to subjects orothers Review serious adverse events including death Comment on outcome of the event or problem and the relationship to the study Concur or non-concur with details of the report provided by the study investigator
Coordinating Investigator	Participate in clinical monitoring activities Facilitate implementation of study across sites Conduct intial site visits Conduct subsequent site visits if needed
DSMB	Review and approve the protocol Identify logistic issues that may pose problems with the study Ensure the safety of the trial by monitoring adverse outcomes, reports of unanticipated problems involving risk to participants, serious adverse events and death events as they occur

7. Communication of Monitoring Results
    a. Monitoring results will be communicated to study sites quarterly via email
    b. Severe data quality or study conduct issues will be reported to the Coordinating Investigator and study PI upon their discovery. A telephone meeting with the site Investigator will be scheduled as soon as possible to discuss the issues and determine a corrective action plan

8. Management of Noncompliance
    a. Any site that has repeated severe issues in data quality or conduct of the study will be reported to the Steering Committee
    b. Sites having this type of difficulty may be terminated from the study for noncompliance

9. Ensuring Quality Monitoring
    a. This Clinical Monitoring Policy will be provided to all those involved in the monitoring of this study