STEM CELL LABORATORY (STCL)

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CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Manual of Procedures (MOP)

A randomized trial of low versus moderate exposure busulfan for infants with severe combined immunodeficiency (SCID) receiving TCRαβ+/CD19+ depleted transplantation: A Phase II study by the Primary Immune Deficiency Treatment Consortium (PIDTC) and Pediatric Blood and Marrow Transplant Consortium (PBMTC)

PIDTC "CSIDE" Protocol (Conditioning SCID Infants Diagnosed Early) PBMTC NMD 1801

IDE Number: 17595

Version Number: 2.0
Version Date: 20 Nov 2019

Summary of Changes:

Number	Date	Affected Chapter(s)	Summary of Revisions Made:
v1.0 to v2.0	20-Nov-19	5, 7, 10, 11	Minor administrative updates throughout, added Miltenyi account creation information, expanded endotoxin testing requirements, added CRF Completion Guidelines link, clarified Data Quality Management processes of the RCI BMT Central Coordination team.
v0.4 to v1.0	14-Mar-2019	2, 3, 4, 5, 6, 7, 8, 9, 10	Removed research and PK sampling information, as a separate Research Sample Information Guide was created. Various updates for clarification and removal of duplicate information from the

			protocol. Added stem cell product shipment information.

MOP TABLE OF CONTENTS

1. INTRODUCTION TO THE MANUAL OF PROCEDURES

1.1. Purpose

A Manual of Procedures (MOP) is a handbook that guides a study's conduct and operations. It supplements the study protocol by detailing a study's organization, operational data definitions, recruitment, screening, enrollment, randomization, intervention procedures and follow-up procedures, data collection methods, data flow, Case Report Forms (CRFs), and quality control procedures. The purpose of the MOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites. Procedures in the MOP should be followed with the same degree of vigor as those documented in the protocol. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

This MOP is to be used as a reference document for policies and procedures related to the study entitled: A randomized trial of low versus moderate exposure busulfan for infants with severe combined immunodeficiency (SCID) receiving TCRαβ+/CD19+ depleted transplantation: A Phase II study by the Primary Immune Deficiency Treatment Consortium (PIDTC) and Pediatric Blood and Marrow Transplant Consortium (PBMTC).

All staff members participating in the conduct of this study at participating institutions will be required to have ready access to the MOP and be familiar with its contents.

1.2. Updating and Version Control

The MOP is a dynamic document that will be updated throughout the conduct of a study to reflect any protocol or consent amendments as well as the refinement of the CRFs and study procedures. As sections/chapters are revised, the MOP version information and date on the cover page and Table of Contents will be updated; the Summary of Changes table on the cover page will list the chapters that have changed and will include a general summary of those changes.

As the study progresses, the Coordinating Center at the Resource for Clinical Investigations in Blood and Marrow Transplantation group (RCI BMT) within the Center for International Blood and Marrow Transplant Research (CIBMTR) will be responsible for documenting any recommended and approved changes to the MOP. The Coordinating Center will incorporate all of the approved changes and will update the MOP periodically. When the revisions are final, the MOP will be distributed to the site PIs and designated study staff. All clinical sites will be notified that the MOP has been updated via a numbered and dated memo, which will also summarize the changes that were made.

The author of an updated MOP chapter will ensure that all necessary changes are captured in the update and that the document is appropriately up-versioned.

The site PI or designee is responsible for on-site document control of the MOP and for filing updates in a timely manner.

As with all numbered memos, the site PI or designee will ensure local distribution of the memo to study staff along with the updated MOP chapter and that the numbered memo is stored in the site's Regulatory Binder.

If paper copies of the MOP are maintained in the binder, the study coordinator will print and store the updated materials in the binder. Remove the outdated materials from the current MOP section of the study binder, and archive previous versions.

2. ADMINISTRATIVE

2.1. Study Leadership Structure

Protocol Chair:
Sung-Yun Pai MD

Protocol Co-Chair:
Michael Pulsipher MD

Study Statistician:
Brent R. Logan

Protocol Committee

Lauri Burroughs, MD
James Connelly MD
Morton J. Cowan MD
Christopher C. Dvorak MD
Elie Haddad MD
Donald B. Kohn MD
Janel Long-Boyle PharmD, PhD
Luigi D. Notarangelo MD
Richard J. O'Reilly MD
Jennifer M. Puck MD PhD
Troy Quigg DO, MS
Heather Smith
Paul Szabolcs MD
William Tse MD PhD

Additional Scientific Collaborators

Hélène Decaluwe MD PhD
Harry Malech MD

Funding Source: NIAID, National Institutes of Health

Primary Immune Deficiency Treatment Consortium Steering Committee

Morton J. Cowan MD (PI), Donald B. Kohn MD (Co-PI),
Linda M. Griffith, Luigi D. Notarangelo, Jennifer M. Puck, Elie Haddad, Sung-Yun Pai

NMDP Medical Monitor: Linda J. Burns MD

CIBMTR Protocol Officer: Bronwen Shaw MD PhD

RCI BMT Clinical Project Manager: Jenny Vogel
RCI BMT Protocol Coordinator: Briana Person
CHLA Protocol Coordinator: Liz Gourdine
PBMTC Study Manager: Laura Hancock

2.1.1. Roles and Responsibilities

Table 1: Study Roles and Responsibilities

Study Team Member	Role	Address	Email	Phone Number
CHLA – Coordinating Center				
Michael Pulsipher	Sponsor-Investigator Protocol-Co Chair	4650 Sunset Blvd., Mailstop #54 Los Angeles, CA 90027	mpulsipher@chla.usc.edu	*O: 323-361-8840*
Liz Gourdine	Central Study Coordinator	4650 Sunset Blvd., Mailstop #54 Los Angeles, CA 90027	Central email: CSIDE@chla.usc.edu	O: 323-361-6652
Laura Hancock	Contracts and Payments	4650 Sunset Blvd., Mailstop #54 Los Angeles, CA 90027	lhancock@chla.usc.edu	O: 323-361-4506
Boston Children's Hospital				
Sung-Yun Pai	Protocol Chair	One Blackfan Circle Karp Family Research Laboratories Room 08214 Boston, MA 02115	Sung-Yun.Pai@childrens.harvard.edu	O: 617-919-2508
Myriam Armant	Central Lab Director	TransLab - Boston Children's Hospital 61 Binney Street Enders 208 Boston MA 02115	Myriam.Armant@childrens.harvard.edu	O: 617-713-8080
CIBMTR / RCI BMT – Coordinating Center				
Bronwen Shaw	Protocol Officer	9200 W. Wisconsin Avenue Suite C5500 Milwaukee, WI 53226	beshaw@mcw.org	O: 414-805-8293
Jenny Vogel	Clinical Project Manager	500 N 5th St Minneapolis, MN 55401	jvogel@nmdp.org	O: 763-406-8691
Briana Person	Central Study Coordinator	500 N 5th St Minneapolis, MN 55401	bperson@nmdp.org	O: 763-406-4412

Anne Schneiderhan	Clinical Research Assistant	500 N 5th St Minneapolis, MN 55401	aschneid@nmdp.org	O: 763-406-4698
UCSF				
Janel Long-Boyle	Study Pharmacist	600 16th St, Genentech Hall 4N-474F San Francisco, CA 94143	janel.long-boyle@ucsf.edu	O: 415-640-1569

2.1.2. Protocol Committee

The Protocol Committee is co-chaired by Michael Pulsipher and Sung-Yun Pai. Other members include those who are contributing to data analysis. Under the direction of Drs. Pulsipher and Pai this committee is responsible for the overall direction of this study including:

- Responsibility for the general design and conduct of the study
- Preparation of the essential study documents, including the protocol, protocol amendments, MOP, and data collection forms
- Review of data collection practices and procedures
- Changes in study procedures as appropriate
- Appointments to and disbanding of study implementation subcommittees
- Allocation of resources based on priorities of competing study demands
- Review of study progress and implementation of necessary steps to ensure the achievement of study goals
- Review and implementation of recommendations from those responsible for safety monitoring

2.2. Policies and Procedures

2.2.1. Protocol Amendment Procedures

Protocol amendments require approval by the Protocol Co-Chairs, as well as written FDA approval when appropriate (exceptions are when IDE protocols do not affect: (A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; (B) The scientific soundness of the investigational plan; or (C) The rights, safety, or welfare of the human subjects involved in the investigation), and IRB before implementation. Any amendment to the protocol will be adhered to by all study staff and will apply to all subjects once appropriate approval is obtained by the IRB.

2.2.2. Version Control of Study Documents

Version control procedures will be used to manage changes to all study documents. Document dates and version numbers will be printed on the first page of each document at the header or footer of each subsequent page. Draft documents will have a version number 0.X with subsequent major draft changes will have an increase of “0.1”, minor changes can have an

increase of “0.01”. The first final draft will be numbered 1.0 with subsequent final documents will have an increase of 1.0 in the version number.

A list of changes from the previous draft or final documents will be kept. The list will be cumulative and identify the changes from the preceding document versions. The list of changes made to the protocol and consent/parental permission should be submitted to the IRB with the final protocol and consent/parental permission documents.

2.2.3. Communication Plan

Numbered Memos

The objective of numbered memos is to document and communicate important study information to all investigative sites in a consistent manner. The numbering of the memos is intended to facilitate reference to the memos, as well as tracking and archiving of the memos.

Responsibilities

- Protocol Co-Chairs, Protocol Committee, or Coordinating Centers may identify issues that require across-site communication/clarification above and beyond discussion during a Site Coordinator or Protocol Committee meeting.
- Protocol Co-Chairs, Protocol Committee, or Coordinating Centers will identify an author and reviewer(s) for the memo.
- Protocol Co-Chairs or designee is responsible for approving the memo. Approval may be communicated via email from a Protocol Co-Chairs or by signature on a version of the memo itself.
- The facilitators of the Protocol Committee and Site Coordinator Meetings are responsible for including a discussion of each new numbered memo on the agenda for the corresponding meeting.
- The Coordinating Centers or designee will be responsible for the email distribution of the numbered memos.
- All Clinical Investigators and Site Coordinators are responsible for reviewing each numbered memo. In addition, all other individuals identified in the “TO” or “CC” lines of the memo are responsible for reading the memo (i.e., site pharmacists, regulatory coordinator, lab techs, etc.).
- Site Coordinators will ensure that all relevant site staff members are aware of the memo and that all numbered memos are stored in the site’s Regulatory Binder.
- If it becomes necessary to correct a numbered memo, a new memo will be distributed with the same memo number and will include a _Corrected_Date designation (e.g., Memorandum #005_Corrected_20JULY2010). The nature of the corrections will be identified in the header of the memo.
- If a protocol decision changes the guidance in a previous numbered memo, a new numbered memo will be issued and will refer to the numbered memo being superseded.

2.2.4. Clinical Trial Registry/ClinicalTrials.gov

Prior to subject enrollment, the study will be registered with ClinicalTrials.gov. Tabular summary data will be reported on the website after meetings of the DSMC; with information including

participant progress, baseline characteristics, any outcome analyses and adverse events exceeding a frequency threshold.

2.2.5. Qualifications

All CVs, licenses, and documentation of both Good Clinical Practice and Human Research Subjects' Protection training for participating site investigators and staff will be filed in the Trial Master File and the site's Regulatory Binder.

2.3. Safety Oversight Committee

Data and Safety Monitoring will be conducted by the Data Safety and Monitoring Committee (DSMC) of the Pediatric Blood and Marrow Transplant Consortium (PBMTC).

The DSMC is a standing committee, composed of a chair, patient advocate, biostatistician, nurse representative and two bone marrow transplant physicians with procedures and processes as defined in the PBMTC DSMC Charter. The DSMC will review the protocol prior to protocol activation and IRB review, and will continue to review the protocol on a regular basis according to the committee rules.

The DSMC will meet at regular intervals to review all adverse events and deaths and determine whether any patient safety problems necessitate protocol modifications or discontinuation of the trial. The DSMC will also meet on an ad hoc basis if stopping guidelines are met or if unexpected safety events occur that may necessitate protocol suspension or closure. The DSMC will discontinue the review of outcomes when this protocol is closed to accrual.

Before each regularly scheduled DSMC meeting, the RCI BMT will submit a report including tabular summaries of all SAEs and deaths on protocol to date. The report will also include a brief summary of each previously unreported SAE and death, including an assessment of whether the event was unexpected or related to the protocol.

If the DSMC recommends protocol or informed consent changes during the study, the recommendations will be reviewed by the Protocol Co-Chairs and incorporated into the protocol as deemed appropriate. The protocol with incorporated changes will be distributed to the participating sites after approval by the National Marrow Donor Program (NMDP) IRB. It is the responsibility of each site PI to forward the distributed communications from the DSMC to their IRB of record.

2.3.1. Roles and Responsibilities

Members of the Data Safety and Monitoring Committee (DSMC) of the Pediatric Blood and Marrow Transplant Consortium (PBMTC) have been selected because they possess the clinical expertise and knowledge of the design, monitoring, analysis, and ethical issues of the clinical research projects that are necessary to protect participant safety and conduct a scientifically rigorous study within the population of bone marrow transplant donors and recipients. The DSMC members must also ensure that they have no direct or indirect financial interest by signing a Conflict of Interest statement.

(http://www.ninds.nih.gov/research/clinical_research/policies/dsm.htm).}

2.3.3. Membership

Table 2: PBMTC DSMC Roster

Paul Martin, MD - Chair Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North Seattle, WA 98109 Ph:(206) 667-5000 pmartin@fhcrc.org	Mitchell Horwitz, MD – Adult BMT Physician Duke University Medical Center Division of Hematologic Malignancies and Cellular Therapy/BMT 2400 Pratt St. DUMC 3961 Durham, NC 27710 Ph: 919-668-1045 fax: 919-668-1091 mitchell.horwitz@duke.edu
John Levine, MD – Vice Chair University of Michigan 1500 E. Medical Center Drive 5303 Cancer Center Ann Arbor, MI 48109-5914 Ph: 734-936-8456 fax: 734-936-8788 jelevine@med.umich.edu	Jennifer Schneiderman, MD, MS – Pediatric BMT Physician Ann and Robert H Lurie Children's Hospital of Chicago 225 E Chicago Ave Box #30 Chicago, IL 60611 Ph: (312) 227-4865 fax: (312) 227-9756 jschneiderman@luriechildrens.org
Paul Haut, MD - Pediatric BMT Physician Indiana University 705 Riley Hospital Drive RI 1960 Indianapolis, IN 46202-5225 Ph: (317) 944-8784 fax: (317) 948-0616 phaut@iuhealth.org	Nancy Barbach, LCSW-R – Patient Representative The Steven and Alexandra Cohen Children's Medical Center of New York 269-01 76th Avenue, Room 255 New Hyde Park, NY 11040 Ph: (718) 470-3460 fax: (718) 343-2961 nbarbach@nshs.edu
Jerelyn Moffet, RN, MS, CPNP – Nurse Representative Duke University Medical Center 2301 Erwin Road Durham, North Carolina 27705 Ph: (919) 684-8111 jerelyn.moffet@duke.edu	Muna Qayed, MD, MsCR – Pediatric BMT Physician Children's Healthcare of Atlanta 1405 Clifton Road NE Atlanta, GA 30322-1062 Ph: (404) 785-1200 muna.qayed@choa.org
Dorothy Vawter, PhD – Patient Representative Minnesota Center for Health Care Ethics 1890 Randolph Ave St Paul, MN 55105 Ph: 651-308-2220 vawter@mnhealthethics.org	Meenakshi Devidas, PhD - Statistician University of Florida 6011 NW 1st Place Gainesville, FL 32607 Ph: 352-273-0551 fax: 352-392-8162 mdevidas@cog.ufl.edu

2.3.4. Frequency of Meetings

The DSMC will meet to review the protocol at least twice per year, unless otherwise agreed upon by the DSMC and Protocol Co-Chairs. The purpose of these meetings will be to review the conduct of the trial to date and to assess safety as determined primarily by the frequencies of serious adverse events, deaths or premature discontinuation of protocol schema because of toxicity among the participants.

Participants in these meetings will include all available members of the DSMC and the PBMTC Manager who will keep minutes. At the discretion of DSMC members, the protocol chairs and statisticians may participate in discussion of the overall protocol progress and safety data during

open sessions. Deliberations regarding DSMC recommendations will be conducted during closed sessions that include only DSMC members and support staff. DSMC members who have a conflict with a protocol will be excluded from these deliberations.

The DSMC chair may call ad hoc meetings of the DSMC, as needed. The DSMC chair will notify other DSMC members to determine whether an ad hoc teleconference should be held.

3. REGULATORY

3.1. Regulations and Regulatory Bodies

This protocol shall comply with ICH and GCP guidelines including the Office of Human Research Protection (OHRP) regulations which include the relevant parts of 45 CFR part 46 : Protection of Human Subjects (the Common Rule) and agree to the Terms of the Health and Human Services (HHS), OHRP Terms of the Federalwide Assurance (FWA). Given that this clinical trial is being conducted under an FDA IDE application must comply with relevant parts of CFR Title 21:

Title 21, Part 50,	Protection of Human Subjects
Title 21, Part 54,	Financial Disclosure by Clinical Investigators
Title 21, Part 56,	Institutional Review Boards
Title 21, Part 812,	Investigational Device Exemptions

3.2. Federal Wide Assurance Documentation

Documentation of the following information will be stored in the sites' Regulatory Binder and will be collected by RCI BMT prior to site activation:

- IRB name
- IRB OHRP registration number
- IRB notification of protocol approval
- Federal-wide assurance number for institutions, sites, and other engaged participants

3.3. Protection of Human Subjects

Written Informed Consent/Parental Permission (as required) must be obtained from each participant at the beginning of the Screening Visit before any participant data can be collected.

3.3.1. Informed Consent / Parental Permission Process

A current, IRB approved copy of the Informed Consent form must be used. Depending on the local IRB, this may mean a stamped copy, rather than the submitted copy. Individuals who sign the informed consent must be those who are recognized by the local IRB as being able to do so. Original signed consent/permission forms must be retained by the local site in the site's study file along with documentation of informed consent/parental permission.

3.3.2. Documentation of Consent / Parental Permission

The International Committee on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines require that the participant or legal representative receive a copy of the signed and dated consent documents. The source documents should indicate version and version date of consent documents used, date of form approval, name of person obtaining consent, the date of signing, and confirmation of the following:

- The informed consent form was signed before any research procedures were performed.
- The participant or parent/guardian was given the opportunity to read the consent and ask questions.
- The participant or parent/guardian was consented in their primary language.
- The participant or parent/guardian verbalized understanding of the informed consent information.
- If applicable, a copy of the signed consent form was given to the participant or parent/guardian.

3.3.3. Translation of Consent and Parental Permission Documents

In order to meet 21 CRF 50.20 informed consent documents and the informed consent process must be conducted in language understandable to the subject. Sites will be required to meet their local IRB standards for accurate translation of whole consent documents or use of short forms.

3.3.4. Changes to Informed Consent Documents

If there is a change in any of the study procedures that may affect the participant, the consent document must be revised and again approved by the Coordinating Centers and the local IRB. Subjects who were enrolled in the study prior to such changes must sign the amended consent document if that change will affect the study participant, previously consented.

3.3.5. Re-consenting for Protocol Changes or Safety Updates

If a consent document is revised due to changes in study procedures, subjects who were enrolled prior to the change, but are affected by the change, will be informed of the changes and will sign the amended consent document. If a consent document is revised due to changes in the risks or safety of the study, all active participants must sign the revised consent.

3.3.6. HIPAA Privacy Rule

Local sites, under the regulation of their IRB must also obtain an Authorization for PHI Used and Disclosures. This authorization must include:

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure
- The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure
- A description of each purpose of the requested use or disclosure
- Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository)
- A statement of the individual's right to revoke Authorization and how to do so, and, if applicable, the exceptions to the right to revoke Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.

- Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
- A statement of the potential risk that PHI will be re-disclosed by the recipient and no longer protected by the Privacy Rule. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.
- Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided

3.4. Regulatory Documents

Regulatory Documents are those documents that individually and collectively permit evaluation of both the conduct of a clinical trial and the quality of the data produced.

Non-subject specific site documents will be filed in the study-specific Regulatory Binder.

3.4.1. Required Documents

The following Regulatory Documents must be retained at the study site, must be accurately maintained, and may be verified during study monitoring visits:

Site-specific documents include, but are not limited to:

- The protocol and all protocol amendments
- All versions of IRB approved consent documents
- IRB documentation, approvals, and correspondence
- Investigator Agreements
- Financial disclosure forms
- Study communication
- Delegation of Authority log
- Documentation of clinical research and study training
- Research sample manifests
- Serious Adverse Events (SAEs)/Unanticipated Problems
- Protocol deviations
- Documentation of clinical site monitoring visits

Subject-specific documents:

- Source documents (e.g., lab reports, ECG tracings, x-rays, radiology reports, etc.)
- Signed consent documents

3.4.2. Document Maintenance

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH or for minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever comes later.

These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor-investigator, through the CHLA Coordinating Center. The sponsor-investigator will inform the site investigators when these documents no longer need to be retained.

4. SITE QUALITY MANAGEMENT PLANS

4.1. Informed Consent

All subjects in this study, whether recipient or donor, or their designee must provide informed consent or parental permission prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person obtaining the subject's consent prior to the subject's entry into the study, must be maintained in the site's study files. Consent forms obtained from NMDP unrelated donors must be maintained in the donor's Donor Center files.

4.2. Data Management

See MOP section 11 Data Management.

4.3. Research Specimen Management

Research studies on this protocol will be centralized. All research studies will be processed and distributed from TransLab (Director, Myriam Armant PhD) at Boston Children's Hospital.

For more detailed information see the CSIDE Research Sample Information Guide.

5. SITE PREPARATION

Prior to site activation the following elements of site preparation will be reviewed and approved by the Coordinating Center:

- IRB-approved clinical research protocol identified by version number and date
- Documentation of IRB approval, including OHRP FWA number, IRB registration number, and IRB name
- IRB-approved consent document that is used to document informed consent, identified by version number, date, or both
- Documentation that the grantee institution and all study staff responsible for the design or conduct of the research have received training in the protection of human subjects and good clinical practice.
- Supplies for study conduct, including CRFs, specimen collection and lab materials, and shipping materials
- Site initiation call and study-specific training
- Contract/grant, technology transfer, clinical trial agreements, and other agreements

5.1. Facilities Requirements

5.1.1. Clinical Research Area

The participating local sites will provide adequate clinical areas to conduct the study.

5.1.2. Secure Document Storage

It is expected that local sites will store all study documents in double locked cabinets and maintain all electronic documents containing PHI password protected.

5.1.3. Laboratory Services

The participating local sites will provide adequate laboratory services required to conduct the study.

5.1.4. Courier Services

Cell Product
To schedule shipment of donor cell product to a central processing lab, please contact Laura Hancock (lhancock@chla.usc.edu) as soon as collection, processing, and infusion dates have been determined between the non-processing and central processing lab.

Research Samples
See the CSIDE Research Sample Information Guide for information regarding shipment of research samples.

5.1.5. Stem Cell Lab Methodologies

See MOP section 7 Stem Cell Processing.

5.1.6. InsightRX Software

The InsightRX platform uses established population PK models on the backend that receives patient-specific factors and clinical covariates entered by the clinical team into a user-friendly, web-based graphical user interface. (Chan et. al. 2017) This allows for a quick and easy initial dose estimation for busulfan, irrespective of the therapeutic target or dose interval and subsequent dose modifications. The primary advantage of this approach, in addition to individualized dosing, is that the drug model may be rapidly updated and refined as new data becomes available, thus, improving the model predictability. Using this approach, the model estimates were updated to better describe busulfan exposure in both neonates and children, resulting in a significantly improved fit as compared to previous population PK models supported by the software.

Access of the InsightRX software requires activation of an account. To request a user account please email the study pharmacologist Janel Long-Boyle, PharmD, PhD at (janel.long-boyle@ucsf.edu). In the email please provide the following:

Full name
Official institute email address
Title (e.g. MD or PharmD)

Study site location
Note in the subject line "Insight-rx C-SIDE Account**"**

Once you are assigned a user account you can log into the platform using the following link: https://pk.insight-rx.com/. Within the platform users will find documentation relating to the InsightRX platform using the following link: http://docs.insight-rx.com/patient-examples.html. Here, users will also find the C-SIDE Manual as well as additional patient examples with TDM data that all user practice of the software.

5.1.7. Miltenyi Account

The manufacturer of the CliniMACs™ device under IDE on this trial, Miltenyi Biotec Inc. provides a reagent and supply discount for study sites registered to the CSIDE study. In order to register with Miltenyi as a CSIDE site, sites must provide their local Miltenyi representative with invoicing and shipping information. This information must include contact names, email addresses, and phone numbers. Prior to ordering reagent and supplies, study sites will also need to provide their local Miltenyi representative with an IRB approval documentation (copy acceptable) and IRB approved local consents, which should include language that states research information will be shared with Miltenyi.

Once a study account has been established for a site, the site may place orders for study reagents and supplies directly with their regional Miltenyi representative.

5.2. Staff Training

5.2.1. Human Subjects Protection and Good Clinical Practice Training

Documentation of Human Subjects Protection Training and Good Clinical Practice Training will be collected according to RCI BMT SOPs.

5.2.2. Protocol Training

All study staff will receive training on all aspects of the protocol, to include:

- Study Objectives
- Inclusion/Exclusion Criteria
- Protocol Deviations
- Graft Processing
- Treatment Timelines
- Subject Visit Schedule
- Screening, Treatment, and End of Study Visits
- Laboratory Evaluations
- Safety Monitoring and Stopping Rules
- Treatment Interruptions or Discontinuation

5.2.3. Clinical Operations

All study staff will receive training in the following areas of clinical operations:

- Communication
- Clinical Research Associate (CRA) Functions and Expectations for Sites
- Site Visits
- Investigator Responsibilities
- Good Clinical Practice (GCP)
- Essential Document Collection and Storage
- IRB Reporting Requirements
- Audits
- Informed Consent Procedures
- Query Process

6. PROTOCOL IMPLEMENTATION

In order to ensure that study procedures are administered in the same way for all participants across all sites, the following sections in the MOP describe the standardized procedures to be implemented.

6.1. Recruitment, Screening, and Enrollment

6.1.1. Recruitment Methods

Recruitment for this study will be conducted as local site investigators provide care to potentially eligible patients in their normal clinical care.

In addition, IRB approved advertisements may be distributed to major transplant centers in the US and the trial may be advertised on websites including the PIDTC website, clinicaltrials.gov, the PBMTC website, and SCID family advocacy groups.

6.1.2. Screening

Patients will be identified at the participating institutions. Patients with a diagnosis of SCID as defined in the Eligibility criteria and in PIDTC protocol 6901 who are believed to be potentially eligible by the site investigator based on diagnosis by screening at birth and lack of a fully matched genotypically identical related donor will be approached for enrollment.

6.1.3. Establishing Eligibility

See protocol for full details.

6.1.4. Assigning Participant Identification Numbers

Participating patients will be assigned a Study Identification Number (Study ID) when they consent for the study. This number will consist of a three letter study identifier (CSD), five numbers indicating the site's CIBMTR Center Number (CCN) and four digits separated by a dash. (CSDXXXXX-XXXX).

The numeric portion of the numbers will be serially assigned in the order the patient is added to Rave. This number will remain with this patient throughout their participation in this study.

6.2. Enrollment Procedures

Baseline studies will be performed after study treatment permission is obtained. Final eligibility review need not be obtained prior to baseline studies. Information for disease and transplant eligibility determination will be entered into the electronic data capture system.

6.2.1. Enrollment and Randomization Process

1. Patient is identified as meeting study criteria by their local transplant physician.

2. Patient's parent/guardian(s) signs the study treatment permission form.

3. Site study personnel complete the Demographics and SCID Diagnostic Information eCRFs in the Rave Electronic Data Capture (Rave) system, including uploading any required and/or relevant SCID diagnostic documentation, at least 2 weeks prior to planned transplant.

4. RCI BMT staff distribute SCID diagnostic data and uploaded documents to CSIDE Eligibility Review Committee members (protocol chairs and a rotating roster of physicians identified by the protocol chairs), who will determine the patient's protocol disease eligibility.

5. Once the Eligibility Review Committee unanimously determines the patient is disease eligible for the study, this data will be entered into Rave and an email notification will be sent to site staff to complete the Inclusion/Exclusion eCRF in Rave.

6. Site staff complete the Inclusion/Exclusion eCRF.

7. If the patient is eligible for study enrollment after the completion of the Inclusion/Exclusion form, an email notification with the patient's enrollment date will be sent to site study staff and RCI BMT staff.

8. RCI BMT staff will then randomize the patient to one of the study arms. Once the randomization assignment is entered into Rave, site staff will receive an email notification of the randomization outcome.

6.3. Requesting an NMDP Donor to Participate in This Study

Once an NMDP donor is identified as the preferred donor for a patient participating in this study, a Workup Request must be placed via the standard NMDP procedures. A Request for NMDP Donor to Participate in a Research Study form (see Appendix II for an example) must be submitted simultaneously with the Workup Request to the NMDP Case Manager.

If you do not have a Request for NMDP Donor to Participate Research Study form on file, please request one from cside@nmdp.org.

Please complete section 1 of the form in full. Complete Section 1B as follows:

NOTE: The Volume/Collection Tubes required are dependent on whether the donor is to a IL2RG/JAK3 cohort patient or to a RAG1/RAG2 cohort patient. Please only specify the volume and tube types for the applicable cohort.

IL2RG/JAK3 Cohort

Required tubes:

- 10mL PURPLE (EDTA)
- 10mL GREEN (NA+ Hep)

RAG1/RAG2 Cohort

Required tubes:

- 10mL PURPLE EDTA

Timing of donor blood collection	Volume/Collection Tubes	Shipping Requirements
• Pre-collection **OR** • At donation	• 10mL GREEN (Na+Hep) • 10mL PURPLE (EDTA) **OR** • 10mL PURPLE (EDTA)	**Packaging: RT** **Ship to: Other:** ATTN Myriam Armant TransLab Boston Children's Hospital 61 Binney Street Enders 208 Boston MA 02115 Phone: 617-713-8085

6.4. Detailed Description of the Study Intervention

See protocol for full details.

6.5. Detailed Description of Study Procedures

See protocol for full details.

7. STEM CELL PROCESSING

Stem cell processing using the CliniMACS™ device will be performed in the Stem Cell Laboratory of the treating institution or at one of the five main central Stem Cell Laboratories, depending on institution's geographic location. All cell processing laboratories must be accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) and maintain complete SOPs and procedure records.

Processing of cells using the CliniMACS™ will occur in accordance with the laboratory SOPs and using aseptic technique.

7.1. Obtaining *ex vivo* T cell receptor (TCR) αβ+CD3+/CD19+ cell Depleted PBSC

See protocol section 6.2.2 for full details.

7.2. Quality Assurance of Cellular Product

Only trained stem cell processors will process the cell products. Each local site PI is responsible to ensure that stem cell processors are adequately trained to operate the CliniMACS™ system according to manufacturer and study specifications.

Each site will be asked to provide an SOP or other documentation outlining their labeling and product tracking system to ensure that the correct cells are infused into the research participant.

Assays of cell numbers and immunophenotyping will be performed both before cell processing and at critical stages of the process. These values will be recorded according to standard operating procedures of center cell processing facilities. All products will be tested for viability and sterility (culture and gram stain), and the presence of endotoxin. Culture and endotoxin results are not available before infusion of fresh cell products. If the gram stain is positive, the research participant/parent and/or guardian will be informed of this event and of the risks of proceeding prior to infusion. Positive results will be investigated as per the variance procedures of center cell processing facilities. The IRB and FDA will be notified, if at any time after infusion, cell product has been determined to be contaminated or endotoxin results exceed release limits.

Table 3: Central Stem Cell Laboratory Locations

Center	Address	Contact	Email
Children's Hospital Los Angeles	4650 Sunset Blvd Los Angeles, CA 90027	Neena Kapoor	nkapoor@chla.usc.edu
University of California, San Francisco	550 16th Street San Francisco, CA 94143	Sherman Bakabak	Sherman.Bakabak@ucsf.edu
Boston Children's Hospital/Dana-Farber Cancer Institute	Cell Manipulation Core Facility Dana-Farber Cancer Institute 1 Jimmy Fund Way, SM12 Boston, MA 02115	Jerome Ritz Sarah Nikiforow	Jerome_Ritz@dfci.harvard.edu sarah_nikiforow@dfci.harvard.edu
Medical College of Wisconsin	8701 Watertown Plank Road Milwaukee, WI 53226	Bryon D. Johnson	bjohnson@mcw.edu
Children's Healthcare of Atlanta	1405 Clifton Road Atlanta, GA 30329	Muna Qayed Daniel Kota	Muna.Qayed@choa.org daniel.j.kota@emory.edu

7.3. Product Quality Assessment

The laboratory performing processing shall be responsible for product quality assessment. Testing prior to product release for infusion must include:

- Total nucleated cell counts (before, during, and after processing)
- Viability assessment (Trypan Blue and/or 7-AAD) (before and after processing)
- Gram stain prior to product release
- Flow cytometry assessment of minimally: CD3, ab TCR, gd TCR, B cells (CD20 post processing, CD19 or CD20 prior to processing), and NK cells (CD56+)
- Removal of samples for sterility cultures (before and after processing)
- Removal of samples for endotoxin assessment (after processing)

7.4. Sterility

Sterility testing samples are sent to the site's local Microbiology Laboratory for bacterial and fungal cultures. Microbiology Laboratories must be inspected and accredited by the College of American Pathologists (CAP). This will utilize continuous monitoring during the 14 day incubation period. The culture systems at both sites have been validated by the cell processing laboratories for the products being tested.

7.5. Notification for a Positive Test

If a culture is positive, the Microbiology Laboratory notifies the Stem Cell Laboratory Director, Cell Processing Laboratory (CPL) Laboratory Manager or, in their absence, a designee who promptly informs the attending transplant physician. This notification is documented on the hard copy of the test results, and it will include the physician's name, and the date and time of the communication.

If the initial sample from a stem cell product is found to be contaminated, possibly during collection, the Stem Cell Laboratory informs the collection facility. This notification is also documented on the hard copy of the Microbiology test results and it will include the collection center staff member contacted and the date and time the communication. The collection facility is requested to undertake a review of the collection procedure. The Microbiology test results for each stem cell product are filed with the processing records and kept according to SOPs.

Site staff will report a positive culture on the Sterility form. Positive cultures will be reported to the IRB, local and central (NMDP), and the FDA.

Stem cell products will already have been infused, and the treating physician, working with the Medical Director, will respond accordingly, including monitoring of the patient, follow up cultures and treatment as clinically indicated.

7.6. Products Will Be Assessed for CD34+

T cell content (TCRab+, TCRgd+, CD3), and B cell content (CD19 and/or CD20) will be assessed by flow cytometry using validated methods. For the CD34+ determination the laboratory should follow the ISHAGE gating protocol and Laboratory staining and analysis SOPs.

7.7. Release Criteria for Stem Cell Products

- Viability of >70%. For viability <70%, the site PI and transplant physician must be notified
- Negative gram stain.

- Cumulative cell doses include:
  - CD34+ Cells- Minimum 2.0 x 10^6 per kg, Target 5.0 x 10^6 per kg
  - ab TCR+ T cells-No minimum, maximum 5.0 x 10^6/kg
  - CD20+ B cells- None specified.

If the defined doses cannot be met due to processing issues or characteristics of the product, approval by the site PI or, in their absence, by one of the co-investigators is required for release.

7.8. Additional Required Test

Endotoxin testing will performed on a sample of the final infusion product. If the test results can be returned prior to infusion, the site can adjust the infusion rate based on the results of the test to be >5 EU/kg/hr. If the results of this test will not be available until after the product has been infused, the site must infuse the product at a slow rate (over 4 hours). This rate maximizes the chance that all infusions will result in endotoxin infusion rates <5 EU/kg/hr. If the endotoxin values are >5 EU/kg of the recipient weight the PI must be notified.

7.9. a/b TCR and CD19 Depletion

Processing consists of the following steps:

- Stem cell product washed to remove platelets
- Biotin-labeled ab TCR reagent is added for 30 minutes at room temperature
- Antibody reagent removed by washing (X2)
- Anti-Biotin and CD19 bead reagents are added for 30 minutes at room temperature
- Reagents removed by washing
- Product is applied to the tubing set on the CliniMACS™ device and depletion program is started
- The ab TCR/CD19 depleted fraction is collected and adjusted for infusion based on flow cytometry analysis

Cell numbers and volume of reagents and product are as per the CliniMACS™ manual. Wash steps all use CliniMACS™ buffer with HSA, and may be performed using a bag method, or using an automated cell washer per laboratory protocols.

7.9.1. *Optional CD34+ Selection to Boost CD34+ Dose*

See Protocol section 6.2.2 for full details.

7.10. Volume and Formulation of Final Product

The goal will be to provide fresh (non-cryopreserved) product for infusion. The product is infused in the processing buffer (phosphate buffered saline with EDTA and a final concentration of 0.5% human serum albumin or equivalent according to Manufacturer's Brochure and Lab SOPs). If concentration/volume reduction is required, after centrifugation the product will be re-suspended in 0.9% Sodium Chloride Injection USP with 5% human serum albumin or equivalent according to Laboratory SOPs.

7.11. Cryopreservation of the Cell Product

In rare instances, donor timing will require cryopreservation of the cell product. In this case, the product will be cryopreserved after processing according to relevant BMT SOPs and thawed at the time of infusion. For cryopreservation, the TCRab/CD19 depleted products are combined with equal volumes of a cryoprotectant containing 20% Dimethyl Sulfoxide (DMSO) in 5% Human Serum Albumin (HSA), or equivalent according to Laboratory SOPs. After the addition of the 2X cryoprotectant to an equal volume of the cell suspension (1:1) the final concentration of DMSO

will be 10%. The products then undergo automated controlled rate freezing with recording of the freezing curves and is stored in the vapor phase of liquid nitrogen in a monitored and alarmed freezer.

7.12. Completion of Processing and Delivery for Infusion

Once release testing is completed, the product label is completed and the product is transported by the laboratory to the infusion site in a validated transport container. Accompanying forms will those specified by laboratory SOPs and in accordance with FACT requirements, including a summary of records used for donor eligibility determination.

Prior to transfer to the infusion team, the product is to be examined by an infusion team member and the processing laboratory staff member to confirm identity of the recipient and the product, observation of the product and product container for appearance, and confirmation of all information on the product label. This transfer must be documented.

Infusion information (date and times, identity of infusion team member, etc.) must be recorded on forms as provided by the laboratory, or in the electronic chart record and must include any adverse events associated with infusion.

8. STEM CELL PRODUCT SHIPMENT

8.1. Non-Processing Sites

Please reference the contract between your site and the central processing lab to determine the logistics of scheduling dates for collection, processing, and shipment. Contact Laura Hancock (lhancock@chla.usc.edu) to schedule courier pick-up and drop-off both before and after cell processing.

8.2. Central Processing Labs

For stem cell product shipment details, please reference:

- Appendix III: Central Lab Processing Standard Operating Procedure
- Appendix IV: Packaging Instructions for Credo
- Appendix V: Credo User Guide
- Appendix VI: Temperature Monitoring Device (TMD) User Guide

8.3. NMDP Donor Product Shipment from Apheresis Centers

8.3.1. Local Lab Processing of NMDP Donor Product

Request NMDP donor product per standard procedures. No additional study-specific shipment processes needed.

8.3.2. Central Lab Processing of NMDP Donor Product

Work with NMDP Case Management and the central processing lab to determine dates for product collection and processing. Request NMDP donor product to be delivered to central processing lab and contact Laura Hancock (lhancock@chla.usc.edu) to schedule courier service from central processing lab to your site.

Shipment Leg	Courier Coordination Group
NMDP Apheresis Center to Central Processing Lab	NMDP Logistics
Central Processing Lab to Transplant Center	Laura Hancock/QuickStat

9. SPECIMENS AND LABORATORY MANAGEMENT

9.1. Standard Clinical Care Studies

Standard clinical care studies on this protocol will be performed locally and include:

- CBC and differential
- Busulfan pharmacokinetics (see Research Sample Information Guide for details)
- Phenotypic characteristics of graft
- Lymphocyte subsets
- Proliferation to PHA
- IgG
- IgA, IgM, IgE
- Measles IgG

For information regarding the schedule of standard clinical care studies, please see protocol Section 8 (Study Schedule). Results of these studies will be reported in Medidata Rave.

9.2. Research Specimen Collection

Research studies on this protocol will be centralized. All research studies listed in Table 4 of the MOP will be processed and distributed from TransLab (Director, Myriam Armant PhD) in Boston Children's Hospital.

Whole blood samples should be obtained using institutional SOPs.

Please reference the Research Sample Information Guide for information regarding:

- Overview of required samples
- Research sample collection supplies and labeling
- Sample processing
- Sample shipment instructions and manifest
- Related donor sample kits
- Pharmacokinetic sampling

9.3. Research Sample Collection by Timepoint for Patients

Table 4: Research Sample Collection Schedule with Volumes in Milliliters

		Baseline	Conditioning							Day 0 (infusion of cells)	7 days	14 days	30 days	42 days	60 days	100 days	6 months	9 months	12 months	2 years	3 years
			day -9 (peak ATG)	day -8 (peak and trough ATG, trough IL-7)	day -7 (peak ATG, IL-7)	day -6	day -5	day -4	day -3												
Research testing	ATG pharmacokinetics and IL-7 levels	0.5	0.5	1.5	1					1	1	1		cells pulled from chimerism sample							
	Thiotepa levels				1																
	Fludarabine levels					2															
	Extended lymphocyte phenotyping	2														2	2		2	2	
	Lineage specific chimerism	buccal swab												2		2	2		4	4	
	Tetanus IgG																	Pre- and post-vaccination according to 6.3.2			2
	CD34+ cell chimerism																			5	
	Plasmablast differentiation	3															3		3	3	
	B cell receptor repertoire	3																5		5	
	Exhaustion panel																10		10	10	
	EBV B cell line	3																			
	TREC	0.5																	0.5	0.5	
	Tolerance studies																		5	5	
	Bank serum	1														1	1		1	1	
	Bank peripheral blood mononuclear cells (PBMC)	2.5														3	3		3	3	

Purple top EDTA tube
Purple top EDTA tube, only for RAG1/2
Purple top EDTA tube, only for IL2RG/JAK3
Green top sodium heparin tube
Green top sodium heparin tube, only for IL2RG/JAK3
Red top or serum separator tube

10. SAFETY ASSESSMENT AND REPORTING

Allogeneic hematopoietic cell transplantation (HCT) is an intrinsically complex procedure associated with a variety of previously well-described adverse events, most of which are non-serious without long-term sequelae. Therefore, for this study, adverse events (AEs) requiring expedited reporting will be limited to Serious AEs and Unanticipated Problems as defined in this section. For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

- There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment;
- There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE;
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures

10.1. SAE and Unanticipated Event Reporting

An adverse event is defined as a serious adverse event (SAE) when the AE 1) results in death, 2) is considered life-threatening, 3) results in hospitalization or cause the prolongation of hospitalization, 4) results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, 5) leads to a congenital anomaly, or 6) represents a significant medical condition which, without urgent medical intervention, would lead to one of the above outcomes. Life-threatening means that the AE represented an immediate threat of death without medical intervention.

It is anticipated that most, if not all, patients on this study will be hospitalized during the course of their allogeneic HCT. Therefore, regarding the hospitalization criterion for seriousness, only AEs that clearly result in prolongation of hospitalization should be considered serious for this study.

Unexpected Adverse Events are those events the nature of which, severity, or frequency are not consistent with the known or foreseeable risk of adverse events associated with the research procedures described in the informed consent document.

Unanticipated problems include unexpected adverse events and also unexpected problems, events, or new information which are not adverse events but which indicate that research participants or others are at greater risk of harm than previously believed prior to recognition of the unanticipated problem.

SAEs will be reported using event terms and severity grading from the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0.

All serious adverse events regardless of attribution relative to study will be reported for review by the Medical Monitor on an expedited basis (see reporting time frames, MOP Section 10.3).

Unanticipated Problems which are related or possible related to study participation and which are:

1) Non-serious AEs but which are unexpected (in terms of unanticipated nature, frequency, or severity) and are thought to represent an increased risk of harm to study participants
2) Events which are not AEs but which add risk to participants or others (e.g. breach of confidentiality –should be reported on an expedited basis.

Unexpected non-serious AEs will be reported via the electronic data capture system. For Unanticipated Problems that do not meet the criteria set forth above should be reported using the Unanticipated Problem Report Form. The same review process will occur for Unanticipated Problems as for SAEs.

Non-serious AEs occurring at expected frequency and severity should not be reported.

10.2. AESI Reporting

Selected grade 3-5 expected adverse events will be collected either as specific data elements related to primary or secondary endpoints, or as adverse events of special interest. Adverse Events of Special Interest (AESI) for this protocol are defined in protocol section 9.1.1.

10.3. Reporting Time Frames and Process

The Principal Investigator will submit reports of unexpected SAEs and other unanticipated problems to FDA and Site Investigators will submit to respective local IRBs in an expedited fashion as required per institutional IRB policy and FDA policy: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051480.htm#adverse.

These events will be reviewed by the FDA and institutional IRBs.

In addition; reports must be submitted in the RAVE Electronic Data Capture system in the following timeframes from when the Local Site Investigator becomes aware of the event:

- **All grade 5 events (deaths)** should be reported within 2 business days.
- **Other SAEs and Unanticipated Problems** should be reported within 3 business days.
- **AESIs in general** should be reported within 5 business days (1 week).
    - Exception: VOD leading to the need of ICU care for organ failure (intubation, dialysis, continuous veno-venous hemofiltration, etc.) should be reported as an SAE within 3 business days.
- **Unexpected grade 3-4 AEs** should be reported within 15 business days (3 weeks).
- **Not reported:**
    - Grade 1-2 AEs that do not meet the definition of SAE.
    - Grade 3-4 AEs that are expected and otherwise are not SAE or AESI.

All SAEs, AESIs, and Unanticipated Problems will be forwarded from the RCI BMT Coordinating Center to the Sponsor-Investigator (Dr. Pulsipher) for review within 72 hours of receipt. These will be reviewed and discussed with the clinical sites within seven days of the report for any SAE, AESI, or Unanticipated Problem.

Upon receipt of the Study PI's assessment the sponsor will notify the appropriate regulatory groups based on the applicable regulations.

10.4. Pregnancy Testing and Counseling

Pregnancy testing should be conducted at screening for donors to exclude for pregnant or lactating individuals.

11. DATA MANAGEMENT

11.1. Data Collection Methods

Data will be recorded by the clinical site investigators as source documentation followed by entry of data into an electronic data capture system. The investigators will maintain adequate case histories of study subjects, including accurate electronic case report forms (eCRFs), and source documentation allowing for adequate monitoring.

Data Capture Methods:

Source Documentation: Source Documentation, including original records of clinical findings, observations, or other activities called for by this protocol, will be retained for each observed data point. These documents will be retained by the local site investigators as described in MOP section 11.2 Source Documentation Requirements.

Case Report Forms: Case report forms will be completed using the electronic database system Medidata Rave. Audit trails of all data changes, security systems, and adequate backup of data will also be implemented. The electronic data capture system will be used for 1) creation of electronic case report forms, 2) resolution of data discrepancies through data queries and checks, and 3) reporting of adverse events and endpoints.

11.2. Source Documentation Requirements

The source document is defined as the first place the data are recorded. The Coordinating Centers will provide selected source document templates, derived from the CRFs, to support data collection (See Research Sample Information Guide Appendices IV-VII). However, these templates should only be used if the data are not originally recorded elsewhere. That is, data from one source should never be transcribed onto a worksheet and then subsequently entered into the CRF. This unnecessarily increases the risk of transcription errors.

In some instances, staff might need documentation from their own or other institutions (e.g., laboratory reports or a hospital report for an SAE). In this case, please request a copy of the record from the institution. It is also recommended that copies of records from outside the clinical research site be added to the subject's binder.

All source documents should be completed by the clinician (or other appropriate study personnel). Data entries into source documents should be made in blue or black ink. Corrections should be made with a single line through the entry and the change initialed and dated. Original entries should remain legible (i.e., they should never be erased or covered with correction fluid to obscure the original entry). Late entries (e.g., laboratory results on the Eligibility Checklist) should be initialed and dated at the time entered.

Data should be handled in accordance with GCP, U.S. federal regulations, local regulations (if applicable), and instructions from NIH. All source documents should be filled out completely by the examining personnel or the study coordinator and should be signed by the person collecting the data on that form. The source documents are reviewed, signed and dated by the principal investigators or study staff designated by the principal investigators.

Source documents for subjects who are screened but not enrolled must be retained following the same guidelines as other study source documents.

11.3. Study Forms

Case Report Forms (CRFs) will be produced by the Data Manager in Medidata Rave, the Electronic Data Capture (EDC) system being utilized for this study. Access to the EDC will be granted to trained and qualified staff and investigators at local sites.

11.4. Case Report Form Completion Guidelines

Source documentation data points should be transcribed into the Medidata Rave system as soon as possible to a maximum of one calendar week to ensure accuracy. Full 17-CSIDE CRF Completion Guidelines (CCGs) are available at *https://www.manula.com/manuals/cibmtr/17-cside-crf-completion-guidelines/1/en/topic/getting-started*.

Table 5: Study Form Submission Timeframes

Study-specific form in Rave EDC	Submission timeframes
Demographics	At least 2 weeks prior to the start of conditioning
SCID diagnostic information	
Inclusion / Exclusion	At least 1 week prior to the start of conditioning
Pre-transplant clinical and laboratory evaluations	
Recipient HLA typing	Prior to infusion date
Donor HLA typing	
Donor forms • Donor demographics • Donor workup • Related donor research samples • Related donor protocol eligibility	
Conditioning regimen forms • Conditioning regimen • Thymoglobulin • Busulfan • Busulfan doses 1-4 • Busulfan source document upload • Thiotepa (RAG1/2 only) • Fludarabine (RAG1/2 only)	Within 7 days of infusion date
PBSC collection	
Graft processing	
Infusion	
Follow-up	Within 7 days of evaluation date for study time point
Idiopathic Pneumonitis Syndrome	
CBC and platelets	
Hematopoietic recovery	
Lymphocyte subsets	
Proliferation to PHA	
Ig replacement	
IgG levels	
IgA, IgM, IgE	

Sample acquisition	

Acute GVHD assessment	If forms are triggered from a Follow-up form response: Within 7 days of evaluation date on corresponding Follow-up form
Chronic or Overlap GVHD forms • Assessment • Organ involvement • Status Therapy	
Infections	
VOD forms • Assessment • Therapy • Maximum severity • Current status	
Tetanus vaccine	
Measles IgG	
Autoimmunity data	
Bone marrow assessment	
Product event	
Sterility	
Adverse event • Assessment • Summary • Meds • Laboratory values • Tests	• All grade 5 AEs: within 2 business days of knowledge of the event • SAEs: within 3 business days of knowledge of the event • AESIs: within 5 business days of knowledge of the event • Grade 3-4 unexpected AEs: within 15 days of knowledge of the event
UPIRSO assessment	Within 3 business days of knowledge of the event
Off study / off protocol	Within 7 business days of study exit event date
Protocol deviation	Within 7 business days of knowledge of the event
Re-consent	Within 7 business days of the event

11.5. Data Review

The RCI BMT staff will review the data forms received from the sites for completeness, internal consistency, protocol compliance and adherence to the protocol. The RCI BMT staff will periodically generate queries and each center will be notified. The queries will identify incomplete, questionable, or inconsistent data. Each center must either correct the data in the CRFs or provide an explanation on the validity of the existing data.

11.6. Data Error Detection and Correction

Sites will be responsible for the accurate and timely entry of data into the EDC. To aid in this process, queries will be generated. Online queries will identify some errors immediately with an error message at the time of submitting the form. These queries should be addressed as soon as possible after generation. Online queries will result when a form is submitted and 1) required information is missing and needs to be corrected, 2) needs to be signed, or 3) is subsequently

edited and a reason for the edit needs to be provided. If a query is left unaddressed in a form, an icon will indicate that form is not complete until the issue is resolved.

11.7. Outstanding and Missing Data and Data Entry Errors

Distinct groups will identify errors in the EDC. The first will be the local site staff as they enter data into the EDC. As unexpected or missing values are entered automatic queries will be generated for immediate response. Subsequent data review will be conducted by the RCI BMT Coordinating Center staff and Study Monitor. These two parties will generate queries when entered data a) do not match source documentation b) sufficiently complex as to be impractical to program as an automatic system check and/or c) requires human judgment. Examples of these cases include misspellings that hinder medical coding and checks that require interpretation of meaning in order to ascertain whether an entry should be queried.

11.8. Data Management Reports

RCI BMT coordinating center staff are responsible for maintaining the electronic data capture system and facilitating the prompt evaluation of reported data particularly adverse events and symptoms. Reports will be generated to show progress reports that will include enrollment, overall, by study section and by sex and race; reason for ineligibility or withdrawal, number of completed visits; number of blood specimens sent to the central repository; and other requested data. A quality control report will summarize inappropriate enrollments, number of missed visits, reason for missed visits, number of out of window visits, and rates of missing data broken down by form.

11.9. Data Quality Management

The RCI BMT Coordinating Center team is responsible for maintaining the electronic data capture system and facilitating the prompt evaluation of reported data, particularly adverse events and symptoms. A quarterly progress report will be generated and will include enrollment, overall, by study section and by sex and race; reason for ineligibility or withdrawal, number of completed visits; number of blood specimens sent to the central repository; and other requested data. A quality control report will summarize inappropriate enrollments, number of missed visits, reason for missed visits, number of out of window visits, and rates of missing data broken down by form. These reports will be reviewed quarterly at a site compliance meeting at the RCI BMT, to include the Protocol Officer.

Weekly, the RCI BMT Coordinating Center team will review reported data for potential safety events, unreported adverse events, and monitoring for stopping rule criteria. This weekly review will also be sent to the protocol Medical Monitor for review and confirmation.

Before each regularly scheduled DSMC meeting, the RCI BMT Clinical Project Manager will prepare a report including tabular summaries of all SAEs and deaths on study to date. The report will also include a brief summary of each previously unreported SAE and death, including an assessment of whether the event was unexpected or related to the study.

11.10. Creating and Distributing Revised Case Report Forms

Case report forms will be completed using the electronic database system Medidata Rave. Audit trails of all data changes, security systems, and adequate backup of data will also

be implemented. The electronic data capture system will be used for 1) creation of electronic case report forms, 2) resolution of data discrepancies through data queries and checks, and 3) reporting of adverse events and endpoints.

11.11. Long Term Storage of Case Report Forms

See MOP section 3.4.2 Document Maintenance.

11.12. Maintaining Data Privacy

All data will be kept in a locked cabinet or electronically secured via password protected applications.

12. MONITORING

Monitoring will be a continuous, ongoing and multifaceted process. This includes external review by the DSMC and IRBs, as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities. A study specific monitoring plan will be developed for each protocol. The purpose of trial monitoring is verification of the following:

The rights and well-being of human subjects are protected;

The reported trial data are accurate, complete, and verifiable from source documents; and

The conduct of the trial is in compliance with the currently approved protocol/amendment (s), with GCP, and with applicable regulatory requirements

12.1. Monitor Responsibilities

Monitoring may be performed by a qualified members of the NMDP audit/monitoring team. While the primary purpose of monitoring is ensuring protocol compliance, monitoring visits also provide a venue for information exchange between the RCI BMT and the site.

The monitors should ensure that the trial is conducted and documented properly by carrying out the following activities: Other activities may be added as needed.

- Verify that the investigator has adequate qualifications and resources to conduct the clinical trial.
- Verify that the staff and facilities have adequate qualifications and resources, including laboratories and equipment (as needed), to properly conduct the trial. .
- Verify that the investigator follows the approved protocol and all approved amendment(s), if any.
- Perform reviews of any SAEs, AEs, Protocol Deviations, Drug Accountability (if appropriate), Informed consents, and queries.
- Verify that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

- Verify that source data/documents and other regulatory documents are accurate, complete, kept up-to-date, and maintained.
- Verify that the investigator, or approved designee, provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

12.2. Monitoring Schedule

The frequency and timing of monitoring visits for each site will be documented in a formalized study specific monitoring plan. The study monitoring plan will be approved by the Protocol Chair, Protocol Officer and PBMTC Chair. At a minimum, the study specific monitoring plan will include the following:

- An overview of monitor responsibilities
- A description of the monitoring schedule which may include indications for initial and subsequent monitoring visits based on accrual and/or sponsoring agency requirements
- Data fields to be monitored including, at a minimum, all inclusion and exclusion criteria and the fields necessary for the primary endpoint of the study
- A description of the monitoring report

12.3. Monitoring Visits

An agenda for site monitoring visits will be provided to the site in advance of the visit.

The site monitor (s) will hold a summary meeting following the completion of agenda with the site PI (if appropriate) and Clinical Research Associate to discuss the monitoring team's observations, review any problems identified, at the visit to the site. A formal written report of the site visit is to be prepared by the site monitor(s) and distributed to the site in a timely manner. A copy of each site report will also be sent to the PBMTC Chair.

Serious violations, such as failure to obtain informed consent, enrollment of ineligible study participants, treatment or pharmacy errors, etc. will result in prompt notification to the RCI BMT Director, Protocol Chair, and the PBMTC Chair. The RCI BMT will analyze each serious violation to determine the impact of the error on study integrity. The issue will be discussed with the center and the center PI will be responsible for supplying an explanation of the violation and corrective action taken.

12.3.1. Site Initiation Visits

If the study requires specific site initiation visits (SIV) to be performed, the following SIV activities may be performed by RCI BMT staff at each center when all of the regulatory and contractual paper work is completed and the study drug and other supplies have been shipped, but before any subjects have been enrolled at that site:

- Detailed discussion of the protocol
- Drug Accountability (if needed)
- Adverse Event Reporting
- Case report form completion
- Monitoring visits

- Regulatory Requirements
- Any other items of importance

SIVs can be performed in person or remotely via web-based training system.

12.3.2. Interim Monitoring Visits (IMV)

Interim monitoring visits will occur in accordance with the approved study specific monitoring plan. At a minimum, the following activities will be performed at each interim monitoring visit:

- Review of regulatory documents
- Review of Adverse events
- Review of protocol deviations
- Review of informed consents
- Review of source documentation

12.3.3. Remote Monitoring

In addition to, or on occasion in lieu of, site visits the protocol coordinator may review accrual reports, CRFs, missing forms and responses to queries. If during the remote monitoring process, the Protocol Coordinator identifies sites with significant problems in these areas the Protocol Chair and Protocol Officer and PBMTC Coordinator and Chair will be notified. The Protocol Chair, PBMTC Chair and Protocol Officer will determine whether corrective action is indicated. The corrective action may include, but not be limited to, discussion with the Principal Investigator, additional training of site personnel, a site visit, or referral to the PBMTC and RCI BMT.

12.3.4. Annual Monitoring Review

At a minimum, annual review will be performed of each site's accrual and monitoring status. If accrual at a site during the previous 12 months did not meet the study specific monitoring criteria but the site accrued at least one patient, an ad hoc site visit will be considered. The Protocol Coordinator, Senior Manager, and Protocol Officer will determine if a visit will occur and when.

12.3.5. Study Close-Out

At study completion, or due to early study termination, it will be determined if a site will require a final on-site visit or close-out may be completed remotely. The Protocol Coordinator, Senior Manager, and Protocol Officer will determine if a visit will occur based upon the sites accrual and timing of the previous monitoring visit.

12.4. Data Quality Assurance

Database quality will be maintained through a variety of analyses that target anomalies, delinquent data and key entry errors. Modifications to the data entry system will be made if the errors occur frequently across centers. If errors are localized within a center, steps will be taken to resolve the problems by additional training to the center or modifications to the data system.

12.4.1. Missing Forms

The determination of missing or delinquent data will be performed at both a form and field level. All missing forms will be identified by form type for each study participant enrolled in a protocol. A missing form will continue to be requested until the form is transmitted. Missing forms or incomplete data may result in site payment hold, communications about delinquency to PBMTC

administration or other measures as applicable. Protocol Coordinator or other RCI BMT staff will review the data for all study participants on a periodic basis.

12.5. Evaluation of Center Performance

The success of multi-center trials depends on high quality performance from the participating sites and careful coordination of effort. It will be the responsibility of the RCI BMT to analyze and review site performance. The RCI BMT is responsible for conducting site-monitoring visits and for the administrative and statistical aspects of site evaluation. For the evaluation process to be successful, it is important to maintain open lines of communication among all parties, periodically review study procedures in order to maintain the highest degree of study integrity and ensure protection of human study participants within an environment that strives for continuous improvement of processes and operations.

Accrual reports for each protocol will be prepared by the RCI BMT and provided to participating sites, the protocol team, and the PBMTC Chair. Centers not meeting accrual goals will be reviewed by the PBMTC Chair, RCI BMT Director, the Protocol Officer, and/or the Protocol Chair to determine the cause of slow accrual and if any corrective processes would improve accrual.

The RCI BMT Protocol Coordinator and/or PBMTC Coordinator will contact centers with serious delinquencies to resolve any training or staffing issues. Serious violations, such as failure to obtain informed consent, enrollment of ineligible study participants, treatment or pharmacy errors, etc. will result in prompt notification to the RCI BMT Scientific Director, Protocol Chair, and the PBMTC Chair. The RCI BMT will analyze each serious violation to determine the impact of the error on study integrity. The issue will be discussed with the center and the center PI will be responsible for supplying an explanation of the violation and corrective action taken.

13. STUDY COMPLETION AND CLOSE-OUT PROCEDURES

13.1. Participant Notification

Participants will not be notified in any way.

13.2. Site Procedures

13.2.1. Data Locking Procedures

Once all final queries have been resolved, the database will be locked to prevent future changes, this will occur prior to the final analysis of the data.

13.2.2. Close-Out Monitoring Visit

The following activities will occur during the close-out monitoring visit:

- Informed consent documentation
- Investigator site file
- Source documentation and CRFs
- SAEs and unanticipated problems reporting

- Laboratory samples
- Records retention
- Verification that study procedures have been completed, data have been collected, and study drug and supplies have been returned to the responsible party or prepared for destruction
- Review of investigator's correspondence and study files against the coordinating centers' records for completeness
- Assurance that all data queries have been completed
- Assurance that correspondence and study files are accessible for external audit
- Reminder to investigators of the ongoing responsibility to maintain study records and to report any relevant study information to the Coordinating Centers.
- Meeting with the site investigators to ensure that they are aware of regulatory obligations and requirements for record retention
- Assurance that the investigator notifies the IRB of study completion and obtains a copy of the notification
- Preparation of a report summarizing study conduct}

13.2.3. Final Study Report (regulated studies only)

Upon completion, a final summary report will be forwarded to the FDA describing the trial, data obtained, participation, events of the study and final outcome of data analysis.

13.2.4. Long Term Storage of Study Documentation

See MOP section 3.4.2 Document Maintenance.

14. APPENDICES

14.1. Appendix I: List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CIBMTR	Center for International Blood and Marrow Transplant Research
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
UPIRSO	Unanticipated Problems Involving Risk to Subjects or Others
US	United States
WHO	World Health Organization

14.2. Appendix II: Request for NMDP Donor to Participate in a Research Study

Email RCI BMT staff at cside@nmdp.org for valid Request for NMDP Donor to Participate in a Research Study form. The below request form is for example purposes only.

Request for NMDP Donor to Participate in a Research Study

Request Form valid: 09/13/2018 through 08/15/2019

Principal Investigator: Sung-Yun Pai, MD (multi-site) **TC Code:** _____ **DC Code:** _____

Name of Study: *A randomized trial of low versus moderate exposure busulfan for infants with severe combined immunodeficiency (SCID) receiving TCRαβ+/CD19+ depleted transplantation: A Phase II study by the Primary Immune Deficiency Treatment Consortium (PIDTC) and Pediatric Blood and Marrow Transplant Consortium (PBMTC) PIDTC "CSIDE" Protocol (Conditioning SCID Infants Diagnosed Early)*

TC Protocol ID Number: PBMTC NMD 1801 **NMDP IRB Number:** IRB-2018-0391

Research Category: 1) Stem cell manipulated under IDE (CliniMACS device)
2) Donor Blood for Laboratory Research
NMDP Approved Volume = **10 mL** (Blood collection instructions in 1B)

Section 1: To be completed by Transplant Center
The following patient is enrolled on this protocol. In this instance, the donor is considered a research subject.

1A. Recipient ID: _____ Donor ID: _____

Anticipated transplant/collection date: _____ - _____ - _____
(Month) (Day) (Year)

1B. ☐ ~~N/A: Protocol does not involve additional blood to be drawn from the donor for research purposes.~~
☒ The specifics of the donor blood collection to be used for research are listed below:

Timing of donor blood collection:	Volume/Collection Tubes:	Shipping Requirements:
☐ Pre-collection	____ mL RED (no anticoag)	Packaging: ☐ RT ☐ 4°C ☐ Other* _____
☐ At Donation	____ mL YELLOW (ACD)	Ship to: ☐ Pre-collect address listed on Prescription
☐ Post-donation	____ mL GREEN (Na+ Hep)	☐ Other* _____
☐ Other _____	____ mL PURPLE (EDTA)	_____
	____ mL OTHER* (specify)_____	_____

*NOTE: The NMDP must approve in advance the use of special collection tubes, packaging or shipping instructions.

TC Coordinator: _____ Date Form Completed: _____

Email or Fax completed Section 1 to Case Manager with work up request at (763) 406-5810

Section 2: To be completed by Donor Center (DC must complete this section and return to Case Management)
Instructions to the Donor Center: The donor listed above is being asked to participate in a research protocol. You will receive, under separate cover, the study documents and consent form. Please counsel the donor during the information session and seek their consent to participate in this study. See Prescription for non-research/clinical blood samples.

Was the donor approached for the study? (i.e., Was study participation presented to donor?)
☐ **Yes**. ☐ Donor consents to participation in research study. ☐ **No**. Reason: _____

Date consent form signed: ☐☐ ☐☐ ☐☐☐☐
(Month) (Day) (Year)

(Also check options below)
i. Donor consents to allow left over blood samples to be stored for future use: ☐Consents ☐Declines
ii. Donor consents to allow genetic testing: ☐Consents ☐Declines

☐ Donor declines participation. *(If study involves additional blood samples [see 1B] do not draw if donor declines.)*
☐ Other: Explain _____

DC Coordinator: _____ Date Form Completed: _____

Email or Fax completed Section 2 to Case Manager at (763) 406-5810

FOR CM ONLY:
- Email completed Sect 1 to Research Admin (IRBStaff@nmdp.org) & DC. Upload to WCC.
- Email completed Sect 2 to TC. Upload to WCC.

 Revision 7 Page 1 of 1

14.3. Appendix III: Central Lab Processing Standard Operating Procedure

Central Cell Processing Lab	Contact	Email
CHLA	Neena Kapoor	nkapoor@chla.usc.edu
CHOA	Muna Qayed Daniel Kota	Muna.Qayed@choa.org daniel.j.kota@emory.edu
Children's Hospital Boston	Jerome Ritz Sarah Nikiforow	Jerome_Ritz@dfci.harvard.edu sarah_nikiforow@dfci.harvard.edu
MCW	Bryon D. Johnson	bjohnson@mcw.edu
UCSF	Sherman Bakabak	Sherman.Bakabak@ucsf.edu

Purpose: To establish a uniform shipping process for all labs that will be acting as a central processing site for the C-SIDE protocol.

Shipping Materials – Credo Cube C4-496 will be provided by QuickSTAT and will be produced by the courier at the time of shipment. See attached document for CREDO packaging instructions.

Shipping Coordination: CSIDE Study Coordinators will coordinate shipment with QuickSTAT and the shipping and receiving sites. The collection center will inform the coordinator of the date of collection.

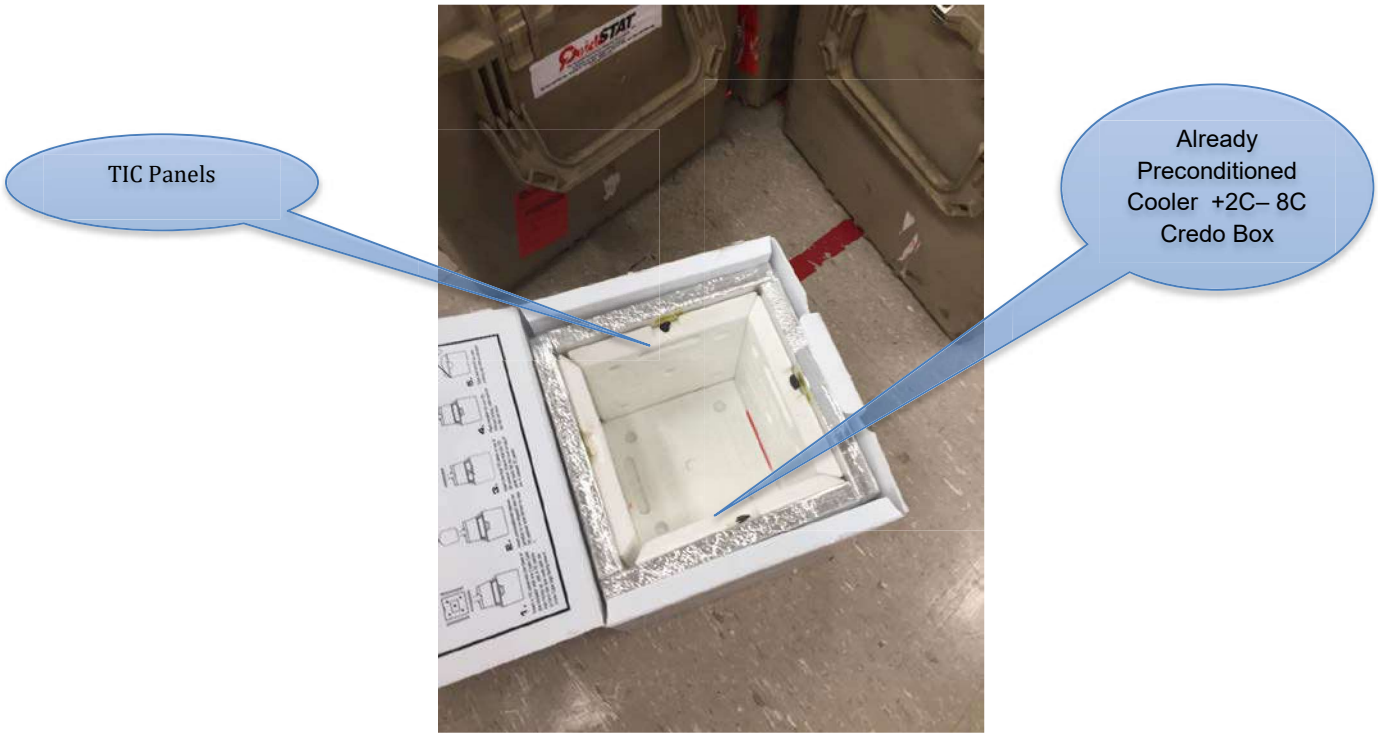
Shipping Temperature: Temperature readouts will be provided by the Temptale IV by sensitec. The receiving location can download the temperature data immediately upon delivery. CSIDE Study Coordinators will be able to track the temperature remotely as well.

Procedure:

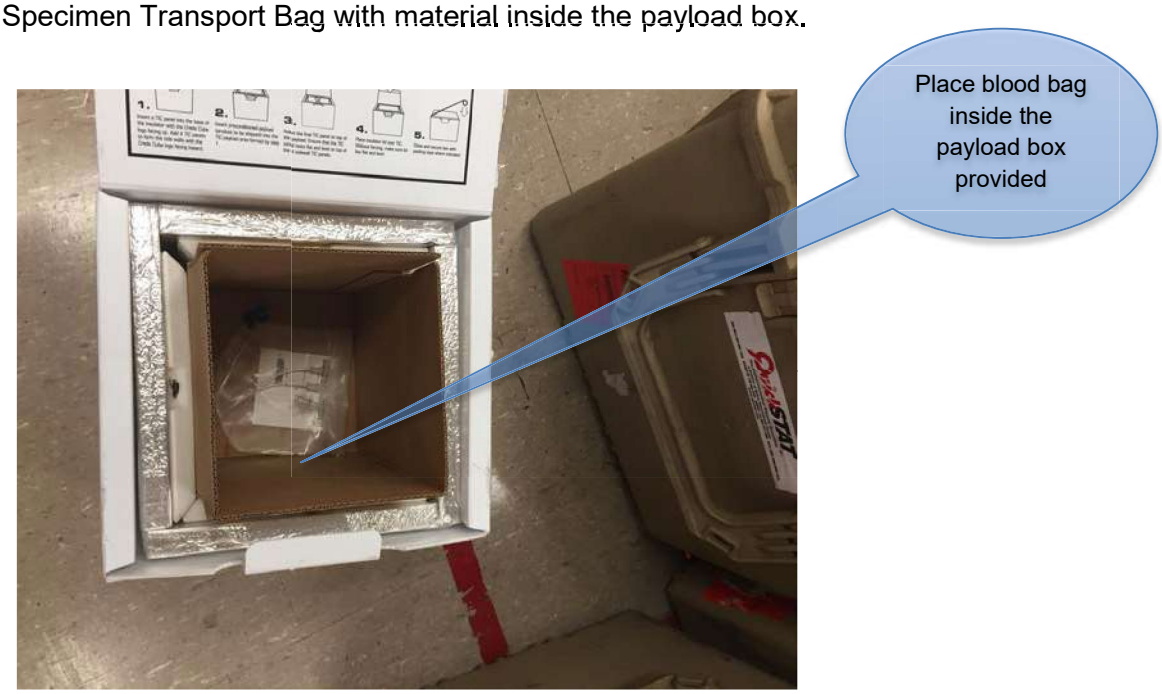
1. Products will be shipped to the central processing lab after collection, for arrival by 8 am the next day at the central lab. Shipping temperature will be +1°C to 10°C and will be continuously monitored by validated data logger device provided in shipper.
2. Central lab will begin processing the product immediately after receipt.
3. Central lab will ship the product back to the initial collection site after completion of processing on the same business day, between 5pm and 8pm local time for delivery at the site by 8am the next morning. Shipping temperature will be +1°C to 10°C and will be continuously monitored by validated data logger device provided in shipper.
4. Central lab will email Certificate of Analysis once completed and prior to the next business day.
5. Lab personnel and Study Coordinator will review data from temp logger and immediately report any temperature excursions. Temp log data will be provided to both the central and receiving laboratories, upon receipt of the shipment.
6. Please contact CSIDE Coordinator: Laura Hancock (323)361-4506, lhancock@chla.usc.edu for any shipping problems /concerns/delays.

14.4. Appendix IV: Packaging Instructions for Credo

1) QuickSTAT driver will bring the Pre-conditioned Credo to site location (empty) Please limit the time the cooler remains open when placing the product inside.



2) Place the Specimen Transport Bag with material inside the payload box.



3) Use appropriate dunnage to secure the blood bag inside the payload box.
Position Temperature Monitoring Device (TMD) inside the payload box (as shown below) next to or on top of the blood bag.

4) Seal the payload box then place the TIC panel on top of the payload box lid in and then the VIP panel on top of the TIC, close the flaps of the Credo Box.
Mark and label the package according to IATA 650 packaging instruction.

14.5. Appendix V: Credo Cube User Guide

Control the whethers

Credo Cube® SERIES 4 USER GUIDE 1

Product Overview

Credo Cube® shippers consist of durable components that meet ISTA 3A transit criteria thereby delivering accurate, long-lasting temperature control allowing for high quality use and look with enhanced operational efficiency.

Innovative TIC® System (Thermal Isolation Chamber) panels with integrated 4˚C phase-change material surround the payload, providing greater temperature performance and overall payload protection.

Modular design provides efficiency in storage and simplicity in preconditioning and pack-out.

* **Nested product configuration is available for longer duration requirements (see Page 3)**

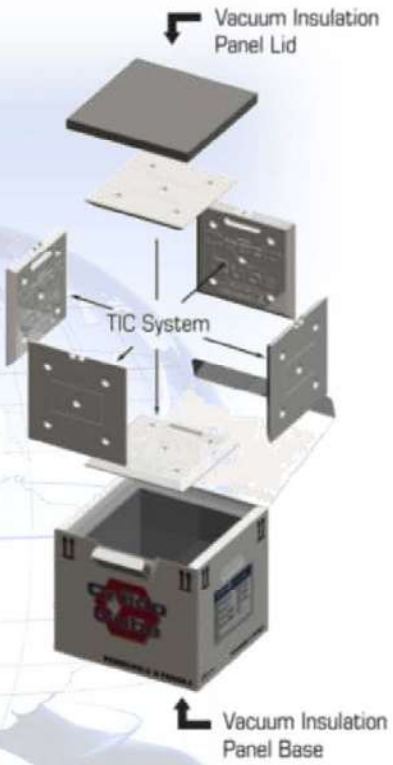
Credo Cube® Benefits at a Glance:

- **Easy quick assembly and single simple pack-out for all seasons.**
- **Reusable patented technology that is recyclable reducing environmental impact.**
- **Enhanced performance and proven payload protection eliminates temperature excursions.**
- **Reduces overall distribution costs.**
- **Longevity of components = lowest cost per use.**

Reduce payload risk.
Reduce distribution costs.
Reduce environmental impact.

Contact Information:
Minnesota Thermal Science
3020 Niagara Lane N • Plymouth, MN 55447
(877) 537.9800 • www.mnthermalscience.com

Standard Product Configuration



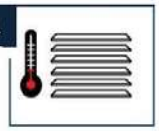
Ensuring Consistent Performance

- ✓ Always precondition TIC System before use according to instructions provided in this User Guide beginning on page 2.
- ✓ Ensure all components are clean and free from damage.
- ✓ Follow assembly instructions printed on inside lid of box outer.
- ✓ After loading, avoid unnecessary opening of container.
- ✓ Ensure both TIC lid and VIP lids are secure before sealing for transport.

USING YOUR CREDO THERMAL PACKAGING SOLUTION (Standard)

2

1

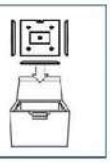


-18°C – 24 hrs

Precondition the TIC® System

- Remove TIC® (Thermal Isolation Chamber) System by pulling open the tab on the front of the corrugate box (or open latches if hard case outer) and removing the insulator lid in order to remove the 6 panels from the insulator base.
- Place the TIC® system in a -18°C freezer, or below for a minimum of 24 hours. Ensure that the TICs lay flat. Freeze times may vary depending on amount of units being frozen and equipment specifications. To ensure TIC was fully frozen, shake panel to verify no liquid can be heard.

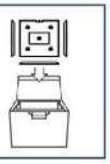
2



Pack Out Preparation

- After freezing, be certain to carefully perform one of the Pack Out Options explained in Pages 5-7.

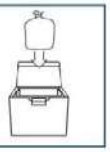
3



Assemble TIC base

- Insert a TIC panel into the insulator base (inner insulator in nested configuration) with the Credo Cube® logo embossment facing up.
- Add 4 TIC panels to form the side walls with the Credo Cube® logo embossment facing inward.

4



Load Payload

- Ensure payload (product to be shipped) is preconditioned at 5°C (+/- 3°C) before loading into the five (5) TIC panel assembly listed above. Do not over pack.
- Add non-insulating filler to fill empty payload space to prevent contents from shifting during transit.
- Place the final TIC panel over the payload area, ensuring the panel lies flat and level without forcing onto the TIC side walls.

5

6

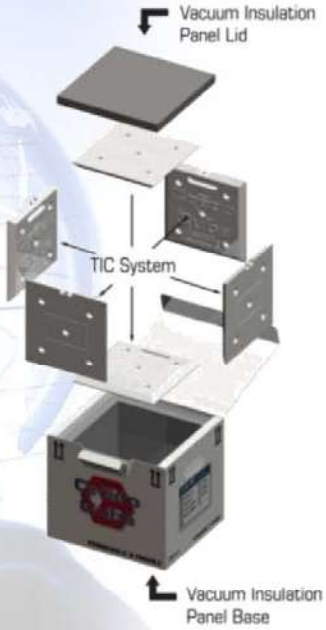
Insert Insulator Lid(s)

- Place the insulator lid over the TIC system making sure it rests flat and level without forcing.

7

Close and secure outer container

- Close and secure outer box (corrugated or plastic) with packing tape where indicated.
- **For Hard Case Outers Only:** Secure latches and use security loop with tamper-proof tie or tag to ensure container is not opened during shipment.



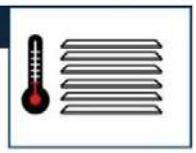
NOTE: In the unlikely event that the container may be exposed to extreme cold conditions (50% or more of the transit time) , precondition as follows: Place the TIC® System in a refrigerator between 4° and 8°C for 4 to 12 hours. Verify that the PCM is liquid by shaking. Refer to www.mnthermalscience.com for additional instructions.

Series 4 User Guide - RF

USING YOUR CREDO® THERMAL PACKAGING SOLUTION – (2" VIP - Nested Configuration)

3

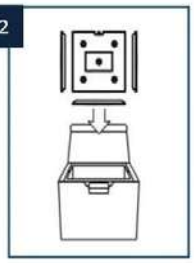
1



Precondition the TIC® System

- Remove TIC® (Thermal Isolation Chamber) System by pulling open the tab on the front of the corrugate box (or open latches if hard case outer) and removing the insulator lid and remove the 6 panels from the insulator base.
- After removing the outer insulator lid, remove the four white corner retention blocks along with the inner insulation lid to expose the 6 panels in the inner insulator base.
- Place the TIC® system in a -18°C freezer (or colder) for a minimum of 24 hours, until frozen hard. Ensure TIC components lay flat. Freeze times may vary depending on amount of units being frozen and equipment specifications. To ensure TIC was fully frozen, shake panel to verify no liquid can be heard.

2



Pack Out Preparation

- After freezing, be certain to carefully perform one of the Pack Out Options explained in Pages 5-7.

Assemble TIC base

- Insert a TIC panel into the insulator base (inner insulator base in nested configuration) with the Credo Cube® embossed logo facing up.
- Add 4 TIC panels to form the side walls with the Credo Cube® embossed logo facing inward.

3

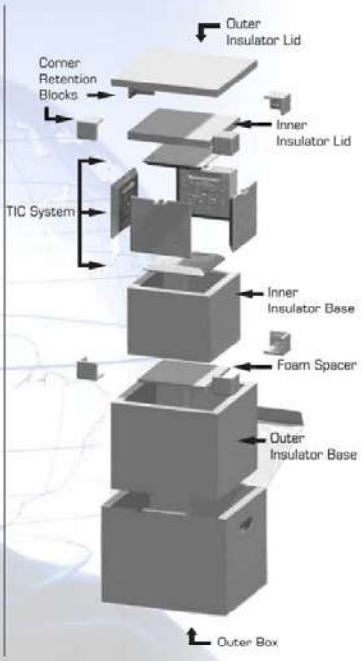
Load Payload

- Ensure payload (product to be shipped) is preconditioned at 5° C (±3°C) before loading into the 5 TIC panel assembly listed above. Do not over pack.
- Add non-insulating filler to fill empty payload space to prevent contents from shifting during transit.

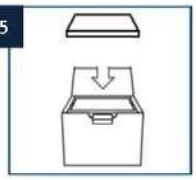
4

Insert TIC Lid

- Place the final TIC panel over the payload area, ensuring the panel lies flat and level without forcing onto TIC side walls.



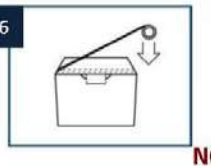
5



Insert Insulator Lid(s)

- Place the insulator lid over the TIC® system making sure it rests flat and level without forcing.
- Place the inner insulator lid over the TIC® system making sure it rests flat and level without forcing. Install the four white corner blocks ensuring the cube logo is facing upwards. Ensure that all four blocks do not protrude above the outer insulator base assembly. Place the outer insulator lid onto the outer insulator base making sure it rests flat and level without forcing.

6



Close and secure outer container

- Close and secure outer box (corrugated or plastic) with packing tape where indicated.
- **For Hard Case Outers Only:** Secure latches and use security loop with tamper-proof tie or tag to ensure container is not opened during shipment.

NOTE: In the unlikely event that the container may be exposed to extreme cold conditions, precondition as follows: Place the TIC® System in a refrigerator between 4° and 8°C for 4 to 12 hours. Verify that the PCM is liquid by shaking.

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CARING FOR YOUR CREDO® THERMAL PACKAGING SOLUTION

4

How to Clean Credo Components

- TIC® System (6 panels): The TIC panels can be cleaned using warm water and soap or alcohol. Sanitization can be performed using isopropyl alcohol and water mixture (typically 70/30 mix alcohol to water) or other salt-based disinfectants.
- Insulator lid and base: Insulator lid and base can be cleaned using a damp towel with soap or a rag with isopropyl alcohol.
- Plastic corrugated outer box: Plastic outer box can be cleaned using a damp towel with a non-abrasive soap or a rag with isopropyl alcohol.
- **DO NOT:**
  1. Autoclave any of the components
  2. Use any organic solvents such as acetone or methyl ethyl ketone (MEK) on any of the components.
  3. Expose any of the TIC components or insulator to extreme heat (+75° C or above.)
  4. Use any abrasive cleaners on any of the components.
- Contact Minnesota Thermal Science for verification if your preferred method is not listed.

How to Perform a Thermal and/or Transit Qualification

Minnesota Thermal Science offers thermal and transit qualification services to industry standards via our thermal laboratory. We also offer a NIST traceable PC-based temperature data logger that fit inside the container and provides accurate, continuous time and temperature data in excel format. We utilize and follow ISTA procedure 5B, ISTA procedure 7D or 7E, which are ASTM D3103 compliant to guide you through your thermal testing process. We recommend ISTA procedure Series 1, 2 or 3, or ASTM D4169 to guide you through your transit testing. Many of our units are already transit tested to ISTA procedure 3A. The certification can be found on the bottom of the box.

How to Inspect and Replace Vacuum Insulation Panels (VIPs)

The Vacuum Insulation Panels (VIPs) in Credo® containers are extremely effective as long as they hold an interior vacuum. Inspect VIP lid and VIP base surfaces periodically. The indicator of a compromised panel is a loss of rigidity. A loose skin or non-rigid panel indicates vacuum loss and the product should be recycled (please refer to page 8 for procedural instruction). Avoid removing VIP base from outer corrugated box. The VIP lid and VIP base should be replaced before the expiration date printed on each panel.

In-Transit Refrigerated Hold

In the event of an unexpected or anticipated delay during transit time the shipper may be placed in a refrigerated environment. By refrigerating the shipper you have effectively "stopped the clock" and the shipping container can be held for an extended time while maintaining the payload between 2° and 8° C. This will preserve the payload should one experience a customs or other form of delivery delay.

Call 1-877-537-9800 for replacement components if needed.

Minnesota Thermal Science • 3020 Niagara Lane N • Plymouth, MN 55447

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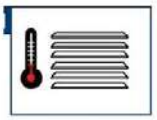
CARING FOR YOUR CREDO® THERMAL PACKAGING SOLUTION

5



OPTION 1: Freezer to Room Temperature (Small volume processing)

Guidelines

After pre-conditioning (step 1 – pages 2 & 3) is complete, the TICs are ready to receive pack out staging-time. The pack out staging-time is the length of time immediately following the TIC removal from the freezer to the time at room temperature wherein the PCM inside will rise to the appropriate operating temperature range.

Diagram 1 is a guideline for the amount of time the TIC® systems require to warm to the operating temperature. [An Infrared temperature thermometer can assist in ensuring the panels reach a safe pack out temperature].

NOTE: Staging-times are based on a freezer temperature of -18°C and a room temperature of 22°C. Panels are not stacked during the staging-time. When you stage TICs the procedure requires ample air flow around all sides of the panels. These times are meant to serve as a guideline and may have to be adjusted based on your individual operating environment.

Staging-Time Reference Chart

TIC Panel Size	Staging-Time Required
5 x 6	35 Minutes
6 x 6	25 Minutes
6.5 x 6.5	30 Minutes
6.5 x 11	30 Minutes
8.5 x 8.5	45 Minutes
9 x 9	35 Minutes
10 x 10	35 Minutes
12 x 12	35 Minutes
12 x 15	40 Minutes
15 x 15	40 Minutes
15 x 18	40 Minutes
18 x 18	40 Minutes

Diagram 1

1 Pre-conditioning times will depend on many variables. The amount of TICs, the TIC orientation, freezer temperatures, freezer compressor strength, and air flow all affect the conditioning times.

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PACK OUT OPTIONS

6

OPTION 2: Freezer to Refrigerator (Large & Small Volume Processing)

This rotational TIC Pack out staging method utilizes controlled freezer and refrigerated temperatures to safely and efficiently condition the TIC® systems.

Guideline:

For larger volumes, the TIC® systems are preconditioned (frozen) according to step 1 on page 2 and 3. When you condition a large amount of TICs the procedure will require ample air flow around the panels to properly freeze the TICs. To facilitate this, MTS recommends using a shelving system or an open mesh bin with spacers positioned between every two rows of stacked TICs. The spacers should be a minimum of 1" thick and should be designed so that there is a sufficient amount of surrounding air flow.

After the bin is loaded, move it into a freezer set to -18°C or colder. Allow a minimum of 24 hours for freeze time. Once the TICs have been properly preconditioned, move the bin into a refrigerated environment (4°C ±2°C) for no less than 48 hours. After the 48 hours in the refrigerated environment the TICs have reached an operating temperature of 2°C and are ready to use.

The procedure for small volume rotational TIC pack out staging is the same as it is for large volume with a few exceptions. In small volume, the TICs can be stacked on top of each other up to 12 panels high. The preconditioning time and minimum refrigerator conditioning time will be different for small volumes. Depending on the TIC size and the performance of the freezer and refrigerator being used, small volume preconditioning times can be 12 to 24 hours and minimum refrigerator conditioning time can be 4 to 30 hours.

An infrared temperature thermometer can assist in ensuring the panels reach a safe pack out temperature. A benefit of the rotational TIC pack out staging method is that once the TICs are in the refrigerated environment they can safely be stored for up to two weeks as long as the average refrigerator temperature is less than 4.5° C **(See Diagram 3).**

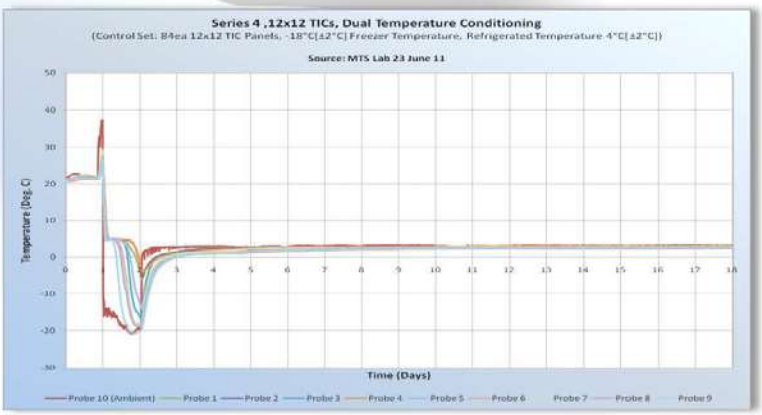

Diagram 3

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PACK OUT OPTIONS

7

OPTION 3: Fully Assembled Pack Out Staging (Large volume processing without refrigeration capabilities)

Guideline:

The TIC® systems are preconditioned according to step 1 on page 1 and 2. After preconditioning is complete, the TICs are packaged into the insulator assembly. Add the insulator lid and close the shipper. Let the shipper sit out at room temperature (22°C [±2°C]) for the time indicated in **Diagram 5**. This will allow the shipper to reach a safe operating temperature of 2°C The shippers should be used shortly after the maximum times listed in **Diagram 5** to ensure maximum thermal performance.

[An infrared temperature thermometer can assist in ensuring the panels reach a safe pack out temperature].

Packout Conditioning Reference Chart

Shipper	Hours Required
4 liter	20-26
12 liter	24-30
16 liter	24-30
17 liter	24-30
28 liter	24-30
56 liter	40-48
96 liter	40-48

Diagram 5

Diagram 4

CONDITIONING ACCESSORY

8

To assist in the preparation and packaging of the MTS shippers we offer a conditioning accessory that works in conjunction with our four Pack Out Preparation option methods. This aide is an accessory designed to make conditioning easier and is not necessary for the proper operation of the shipping system.

Infrared Thermometer (IR gun)

MTS offers an Infrared temperature thermometer for an accurate, quick, and easy reading of the temperature of the TIC system and your product. The IR gun can display in Celsius or Fahrenheit and has a response time of less than one second. It has an accuracy of ±1°C and a temperature resolution of 0.1°C. The IR gun also comes equip with a laser for accurate aiming. The IR gun is calibrated to NIST standards and the manufacture offers a three point calibration certificate for an additional charge.

Procedure:

The Infrared Temperature Thermometer is easy to use. Simply hold the gun about six inches away from your target, squeeze the trigger while aiming the laser dot where you want to read the temperature. When you release the trigger the temperature will display for an additional four seconds. MTS recommends flipping the TIC over (so the side that was down during freezing is up) and taking temperature readings from the side of the center standoff.

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MINNESOTA THERMAL SCIENCE COMPONENT RECYCLING PROGRAM

9

End of Life Component Recycling Program

Minnesota Thermal Science proudly offers a convenient, complimentary recycling service for all Credo® thermal packaging components. Components are specifically designed for reuse and recycle, reducing overall environmental waste. After extended reuse, components will reach the end of their useful life and can be recycled at any of the locations below. Take the next step... **REDUCE, REUSE** and **RECYCLE.**

Directions:
Please separate TIC panels from the VIP insulators and the outer containers. Outer containers can be sent with the VIP assemblies to the VIP Recycling Centers. Outers can also be recycled in-house. Securely palletize the load and clearly mark on every pallet the recycling center header and address as listed below.

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COMPONENT DROP OFF LOCATIONS:

VIP RECYCLING DROP OFF CENTER
Minnesota Thermal Science
3721 Spirit Drive SE
Albuquerque, NM 87106

INTERNATIONAL VIP RECYCLING DROP OFF CENTER
Minnesota Thermal Science
The factory, Rectory Lane
Brimfield, Shropshire SY8 4NX United Kingdom

***NOTE:** Client is responsible for freight.

For more information visit
www.mnthermalscience.com
or **call 877.537.9800**

Series 4 User Guide - RF

SERIES 4 CREDO SHIPPER SPECIFICATIONS MATRIX 10

Product Name	Temperature Range	Payload Dimensions (LxWxH)	Volumetric Capacity	Outer Dimensions (LxWxH)	Tare Weight	Performance (expressed as hours within the temperature range) X = No testing completed			
Description	°C	Millimeters	Liters	Millimeters	Kilo-grams	ISTA Summer No Load	ISTA Winter No Load	ISTA Summer With Load	ISTA Winter With Load
Series 4 3120	2°C - 8°C	129.5 x 129.5 x 129.5	3	317.5 x 266.7 x 266.7	5.8	93.97	161.17	X	X
Series 4 496	2°C - 8°C	149 x 149 x 149	4	317.5 x 266.7 x 273	5.0	65.25	146.03	X	X
Series 4 896	2°C - 8°C	281.9 x 165.1 x 165.1	8	444.5 x 288.9 x 292.1	7.5	76.86	146.08	X	X
Series 4 10120	2°C 8°C	212.09 x 212.09 x 212.09	10	381 x 330.2 x 342.9	10.7	104.72	147.92	X	X
Series 4 1248	2°C - 8°C	226 x 226 x 226	12	431.8 x 387.4 x 412.8	9.3	43.17	144.00	47.58	168.00
Series 4 1296	2°C - 8°C	226 x 226 x 226	12	381 x 330.2 x 342.9	9.9	94.86	146.03	92.42	168.00
Series 4 1696	2°C - 8°C	254 x 254 x 254	16	400.1 x 355.6 x 358.78	11.7	84.67	145.33	84.50	116.25
Series 4 1696 DuraCUBE	2°C - 8°C	254 x 254 x 254	16	444.5 x 444.5 x 412.8	15.3	90.42	145.33	103.83	120.00
Series 4 1696 Pelican Case	2°C - 8°C	254 x 254 x 254	16	457.2 x 419.1 x 431.8	20.5	93.42	138.67	X	X
Series 4 2896	2°C - 8°C	304.8 x 304.8 x 304.8	28	457.2 x 419.1 x 431.8	16.0	103.22	146.03	101.67	144.00
Series 4 2896 Pelican Case	2°C - 8°C	304.8 x 304.8 x 304.8	28	533.4 x 533.4 x 489	24.4	106.33	178.83	X	X
Series 4 4296	2°C - 8°C	457.2 x 304.8 x 304.8	42	612.8 x 412.4 x 422.3	20.0	115.92	159.00	130.50	120.00
Series 4 5696	2°C - 8°C	381 x 381 x 381	56	533.4 x 495.3 x 501.65	24.9	111.75	117.00	X	X
Series 4 9696 Kraft	2°C - 8°C	457.2 x 457.2 x 457.2	96	762 x 654.1 x 711.2	38.1	102.92	X	X	X
Series 4 9696 Pelican Case	2°C - 8°C	457.2 x 457.2 x 457.2	96	685.8 x 685.8 x 660.4	47.7	126.00	146.67	X	X
Series 4 - 2" VIP (Nested Configuration)									
Series 4 4120	2°C - 8°C	149 x 149 x 149	4	381 x 330.2 x 342.9	7.9	102.08	147.25	131.50	147.00
Series 4 12168	2°C - 8°C	226 x 226 x 226	12	444.5 x 406.4 x 406.4	14.4	163.50	170.00	158.75	171.00
Series 4 16168	2°C - 8°C	254 x 254 x 254	16	470 x 426 x 435	14.60	166.08	185.33	X	X
Series 4 28168	2°C - 8°C	304.8 x 304.8 x 304.8	28	533.4 x 495.3 x 501.65	22.8	162.17	171.00	159.67	168.00
Series 4 56168 Kraft	2°C - 8°C	381 x 381 x 381	56			X	X	X	X
Series 4 56168 Pelican Case	2°C - 8°C	381 x 381 x 381	56	685.8 x 685.8 x 660.4	47.6	186.75	235.00	X	X
Operating Room Containers									
Series 4 824OR	2°C - 8°C	281.9 x 165.1 x 165.1	8	406.4 x 260.35 x 381	6.4	16.25	X	23.50	X

Description	°F	Inches	Cubic Inches	Inches	Pounds	ISTA Summer No Load	ISTA Winter No Load	ISTA Summer With Load	ISTA Winter With Load
Series 4 3120	35°F - 46°F	5.1 x 5.1 x 5.1	133	12.5 x 10.5 x 10.75	12.7	93.97	161.17	X	X
Series 4 496	35°F - 46°F	5.9 x 5.9 x 5.9	205	12.5 x 10.5 x 10.75	11.0	65.25	146.03	X	X
Series 4 896	35°F - 46°F	11.1 x 6.5 x 6.5	469	17.5 x 11.375 x 11.5	16.6	76.86	146.08	X	X
Series 4 10120	35°F - 46°F	8.35 x 8.35 x 8.35	582.2	15.0 x 13.0 x 13.5	23.5	104.72	147.92	X	X
Series 4 1248	35°F - 46°F	8.9 x 8.9 x 8.9	705	17.0 x 15.25 x 16.25	20.6	43.17	144.00	47.58	168.00
Series 4 1296	35°F - 46°F	8.9 x 8.9 x 8.9	705	15.0 x 13.0 x 13.5	21.8	94.86	146.03	92.42	168.00
Series 4 1696	35°F - 46°F	10 x 10 x 10	1000	15.75 x 14.0 x 14.125	25.8	84.67	145.33	84.50	116.25
Series 4 1696 DuraCUBE	35°F - 46°F	10 x10 x 10	1000	17.5 x 17.5 x 16.25	33.8	90.42	145.33	103.83	120.00
Series 4 1696 Pelican Case	35°F - 46°F	10 x10 x 10	1000	21.0 x 21.0 x 19.25	45.2	93.42	138.67	X	X
Series 4 2896	35°F - 46°F	12 x 12 x 12	1728	18.0 x 16.5 x 17.0	35.2	103.22	146.03	101.67	144.00
Series 4 2896 Pelican Case	35°F - 46°F	12 x 12 x 12	1728	21.0 x 21.0 x 19.25	53.8	106.33	178.83	X	X
Series 4 4296	35°F - 46°F	18 x 12 x 12	2592	23.75x 16.5 x 17.0	44.2	115.92	159.00	130.50	120.00
Series 4 5696	35°F 46°F	15 x 15 x 15	3375	21.0 x 19.5 x 19.75	54.8	111.75	117.00	X	X
Series 4 9696 Kraft	35°F - 46°F	18 x 18 x 18	5832	30.0 x 25.75 x 28.0	84.0	102.92	X	X	X
Series 4 9696 Pelican Case	35°F - 46°F	18 x 18 x 18	5832	27.0 x 27.0 x 26.0	105.2	126.00	146.67	X	X
Series 4 - 2" VIP (Nested Configuration)									
Series 4 4120	35°F - 46°F	5.9 x 5.9 x 5.9	205	15.0 x 13.0 x 13.5	17.4	102.08	147.25	131.50	147.00
Series 4 12168	35°F - 46°F	8.9 x 8.9 x 8.9	705	17.5 x 16.0 x 16.0	31.8	163.50	170.00	158.75	171.00
Series 4 16168	35°F - 46°F	10 x 10 x 10	1000	18.5 x 16.75 x 17.125	32.2	166.08	185.33	X	X
Series 4 28168	35°F - 46°F	12 x 12 x 12	1728	21.0 x 19.5 x 19.75	50.2	162.17	171.00	159.67	168.00
Series 4 56168 Kraft	35°F - 46°F	15 x 15 x 15	3375			X	X	X	X
Series 4 56168 Pelican Case	35°F - 46°F	15 x 15 x 15	3375	27.0 x 27.0 x 26.0	105.0	186.75	235.00	X	X
Operating Room Containers									
Series 4 824OR	35°F - 46°F	11.1 x 6.5 x 6.5	469	16 x 10.25 x 15	14.0	16.25	X	23.50	X

User Guide Reference Chart

Control the whethers

For more information visit www.mnthermalscience.com or **Call 877.537.9800**

14.6. Appendix VI: Temperature Monitoring Device (TMD) User Guide

TempTale®4 USB

Shipment information without proprietary software and hardware

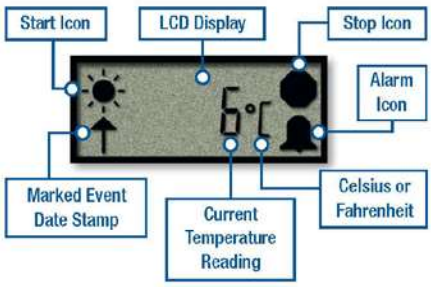
Fast, simple, efficient, and secure cold chain visibility

A large quantity of disparate receiving sites, particularly in the distribution of clinical trial materials and sales representative samples, adds complexity to the shipment disposition process. The administration, setup, and training required to retrieve cold chain data within these elaborate supply chains is often difficult to manage.

The TempTale®4 USB datalogger helps to eliminate these problems by combining Sensitech's industry-leading temperature monitoring technology with USB 2.0 PC communications and a powerful on-board microprocessor that enables access to recorded shipment information without a proprietary desktop software application or hardware reader.

Plug in the monitor to your PC's USB port, and the TempTale4 USB monitor will automatically create a cold chain shipment information report in Adobe® PDF format. Viewable using any Adobe-compatible reader program, the report provides a complete cold chain trip history, resulting in rapid on-site shipment dispositions. Via email or other file sharing capability, every interested party can instantly and effortlessly review shipment information.

In addition, the TempTale4 USB monitor creates an encrypted data file (.ttx format) compatible with Sensitech's TempTale Manager® Desktop (TTMD) PC software and Internet-enabled application, ColdStream® Cold Chain Manager (CCM). The .ttx format data file enables secure data transfer, aggregation, analysis, and storage in support of 21 CFR Part 11 compliance and quality assurance requirements.



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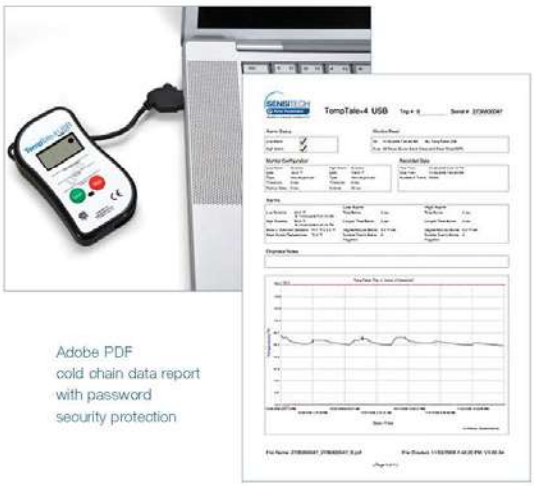
SUPPLY CHAIN VISIBILITY

TempTale.4 USB

TempTale4 USB Specifications	
Temperature Measurement Range	-30°C to 70°C (-22°F to 158°F)
Temperature Accuracy Range	±1.1°C from –30°C to –18°C (±2.0°F from –22°F to 0°F) ±0.55°C from –18°C to 50°C (±1.0°F from 0°F to 122°F) ±1.1°C from 50°C to 70°C (±2.0°F from 122°F to 158°F)
Temperature Resolution	0.1°C/F over full temperature measurement range
Memory Type	Non-volatile 16K EEPROM
Storage Capacity	16,000 data points
Battery Life/Type	1-year run life/3.0v lithium battery
Data Sampling Interval	Programmable from 10 seconds up to a maximum of 2 hours
Water Resistant Housing	NEMA 6 rating (electronic enclosure)
Start-Up Delay	Minimum 0 seconds, Maximum 194 days
LCD Programmable Options	Display current temperature reading, display temp values in °C or °F, Enable flashing of start, stop and alarm icons
Start Up Options	Manual push button or automatic launch
Alarm Function	Programmable high and low limits; alarm is triggered when temperature exceeds set limits
Typical Dimensions	10.0cm L x 5.5cm W x 2.1cm H (3.95" L x 2.18" W x 0.82" H)
Weight	71 grams (2.5 ounces)
Quality Assurance Certifications	CE Mark by TUV; NIST® traceable and 3-point Certificate of Validation; ROHS; WEEE; Validation manual
Software/PC Interface	TempTale Manager® Desktop or ColdStream® Cold Chain Manager Software; Adobe Reader
PC Interface	USB 2.0, A-Type plug
Monitor Recording Options	Single Use



Adobe PDF cold chain data report with password seourity protection

Features and Benefits

- Easy-to-use "plug-n-play" operation
- No proprietary software installed at shipment destination
- Integrated USB connector; no hardware or interface cable required
- Fully independent operation; no PC applications and no retained PC "footprint"
- Automatic generation of Adobe PDF cold chain data report allows prompt on-site decision making
- Automatic generation of encrypted data file enables simple retrieval and email transfer of recorded data to the shipment originator; eliminates the return of the monitor to the originator for data download
- Data file compatibility with Sensitech's software tools permits comprehensive data analysis and record keeping
  - TempTale Manager Desktop – PC-based Windows® application for storing, displaying, analyzing, and printing recorded time-and-temperature data
  - ColdStream Cold Chain Manager (CCM) – Web-accessible data management service for centralized storage and retrieval of cold chain logistics information

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Sensitech Inc. • 800 Cummings Center • Suite 258X • Beverly, MA 01915-6197 • 1-800-843-8367 • +1-978-927-7033 • Fax: +1-978-921-2112 • clientservices@sensitech.com
Sensitech EMEA • Tel: +31 (0)252 211 108 • Fax: +31 (0)252 231 032 • info@sensitech.eu

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Author

Name/Signature	Title	Date	Meaning/Reason
Barbara Waters-Pick (WATER002)		30 Aug 2021, 05:17:12 PM	Approved

Management

Name/Signature	Title	Date	Meaning/Reason
Barbara Waters-Pick (WATER002)		30 Aug 2021, 05:17:28 PM	Approved

Medical Director

Name/Signature	Title	Date	Meaning/Reason
Joanne Kurtzberg (KURTZ001)		30 Aug 2021, 05:41:17 PM	Approved

Quality

Name/Signature	Title	Date	Meaning/Reason
Isabel Storch De Gracia (IMS19)		30 Aug 2021, 06:56:07 PM	Approved

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Sandra Mulligan (MULLI026)		30 Aug 2021, 09:01:33 PM	Approved