Manual of Procedures (MOP)

A Phase II Pilot Study of Donor-Derived *Ex-Vivo* Expanded Natural Killer Cell Infusions in Children and Young Adults with High Risk Acute Myeloid Leukemia Receiving Myeloablative HLA-Haploidentical Hematopoietic Cell Transplant: A Multicenter Pediatric Transplantation and Cellular Therapy Consortium (PTCTC) Study (EXCEL Trial) PTCTC CEL2001

Version Number: 3.0
Version Date: 10DEC2021
PTCTC Study Number: CEL2001

MOP V3.0, 10DEC2021, Summary of Changes

Number	Date	Affected Section(s)	Summary of Revisions Made
1.0	21DEC2021	Throughout	Updated MOP version and date.
2.0	21DEC2021	7.1.3.4 Preparation of the Credo Cube Forms	7.1.3.4 Preparation of the Credo Cube - Forms Section clarified to state sites should only include the EXCEL Study approved forms listed in this section and included in Appendix when shipping specimen in the Credo Cube.
3.0	21DEC2021	7.1.3.4 Preparation of the Credo Cube Packaging	7.1.3.4 Preparation of the Credo Cube - Packaging section clarified to state specimen are shipped at ambient temperature.
4.0	22JUL2022	Throughout	Updated MOP Version and date.
4.0	22JUL2022	8.5 Case Report form Completion Guidelines	8.5 Study Form Submission Timeframes table updated to clarify adverse event reporting.
4.0	22JUL2022	Appendix XI EXCEL Enrollment Request Form	Appendix XI EXCEL Enrollment Request Form updated to provide additional clinical information for EXCEL Leadership review. EXCEL Manufacturing will provide dates for collection based on sites preferred Day 0.
4.0	22JUL2022	Appendix XII	Appendix XII Added two new tables to provide clarification for adverse event reporting timelines.

MOP TABLE OF CONTENTS

SECTION 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, intervention, 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. The 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 Phase II Pilot Study of Donor-Derived *Ex*-*Vivo* Expanded Natural Killer Cell Infusions in Children and Young Adults with High Risk Acute Myeloid Leukemia Receiving Myeloablative HLA-Haploidentical Hematopoietic Cell Transplant: A Multicenter Pediatric Transplantation and Cellular Therapy Consortium (PTCTC) Study (EXCEL Trial).** 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 **Children's Hospital of Los Angeles (CHLA)** will be responsible for documenting any recommended and approved changes to the MOP. The Coordinating Center will incorporate all 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.

SECTION 2: ROLES AND RESPONSIBILITIES

Table 1: Study Roles and Responsibilities

Team Member	Role	Center	Email and Contact Number
Monica S. Thakar	Protocol Chair	Fred Hutchinson Cancer Research Center	msthakar@fredhutch.org (206) 314-1412 (pager) or (206) 987-2000 (Seattle Children's Operator can also send an alpha numeric message)
Hemalatha Rangarajan	Protocol Co-Chair	Nationwide Children's Hospital	Hemalatha.Rangarajan@nationwidechildrens.org (614) 690-1015
Dean Lee	Scientific Director	Nationwide Children's Hospital	Dean.Lee@nationwidechildrens.org (614) 355-3594
Michelle Watts	Project Manager	Nationwide Children's Hospital	Michelle.Watts@nationwidechildrens.org (614) 355-1533
Shane Wellman	Manufacturing Logistics, CBT	Nationwide Children's Hospital	Shane.Wellman@nationwidechildrens.org 614-355-3598
Michael Pulsipher	IND Sponsor-Investigator	CHLA (PTCTC)	mpulsipher@chla.usc.edu (323) 361-8840
CHLA PTCTC Operations Center	All EXCEL Related Communications	CHLA (PTCTC)	EXCEL@chla.usc.edu

2.1 Policies and Procedures

2.1.1 Protocol Amendment Procedures

Protocol amendments require approval by the Protocol Co-Chairs and may require written FDA approval when appropriate. 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.

2.1.2 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. 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.

2.1.3 Communication Plan

2.1.3.1 Numbered Memos

The objective of numbered memos is to document and communicate important study information to all investigative sites in a consistent manner.

2.1.3.2 Responsibilities

- 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.

2.1.4 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.

2.1.5 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.

2.1.6 Safety Oversight Committee

PTCTC DSMC
Hati Kobusingye – Contact
National Marrow Donor Program
hkobusin@nmdp.org

SECTION 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 Federal wide Assurance (FWA). Given that this clinical trial is being conducted under an FDA IND 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 PTCTC 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 (both patient and donor) at the beginning of the Screening Visit before any participant

data can be collected.

3.4 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.

3.5 Documentation of Consent / Parental Permission

The International Committee on Harmonization (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 the 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.

3.6 Translation of Consent and Parental Permission Documents

To meet 21 CRF 50.20 informed consent documents, 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.

3.7 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.

3.8 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.

3.9 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

3.10 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.

3.11 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
- 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)
- Signed consent documents

3.12 Document Maintenance

Study records will be maintained for at least 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 6 years have elapsed since the formal discontinuation of the study, 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.

SECTION 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.

4.2 Data Management

4.2.1 Data Entry

Data collected during this study will be entered into a secure electronic data capture (EDC) system, Medidata Rave®.

4.2.2 Case Report Forms

CRFs will be generated by the PTCTC Coordinating Center for the collection of all study data. Transplant Center Principal Investigators will be responsible for ensuring that the CRFs are kept up to date.

4.2.3 Source Documents

Study personnel will record clinical data in each patient's source documents (i.e., the patient's medical record). Source documentation will be made available to support the patient research record. Study monitors will review entries on the CRFs at regular intervals, comparing the content with source documents.

4.2.4 Data Submission

All data will be collected on CRFs. CRFs will be provided to participating sites by the PTCTC. A primary research data file (research chart) will be maintained at each site and must include copies of required source documentation.

4.2.5 Record Retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents, study-related documents, and the CRFs. Because the length of time required for retaining records depends upon several regulatory and legal factors, documents should be stored until the investigator is notified that the documents may be destroyed. In this study, records are to be retained and securely stored for a minimum of 7 years after the completion of all study activities.

4.3 Research Specimen Management

Research studies on this protocol will be centralized. All research studies will be processed and distributed from Nationwide Children's Hospital.

SECTION 5: SITE PREPARATION

5.1 Pre-Activation

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

- Fully executed master consortium agreement
- Fully executed EXCEL study rider
- IRB approval notice of clinical research protocol identified by version number and date
- IRB-approved consent documents that will be used to document informed consent, identified by version number, date, or both
- Documentation of IRB Name, Address, and Registration number, IRB Member Roster, and OHRP FWA number
- 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
- Completed Form 1572 for Site Principal Investigator
- Completed Financial Disclosure Forms for all investigators
- Signed and dated CVs for all investigators
- Medical licenses for all investigators
- Completed Delegation of Authority log
- Completed Investigator Brochure and Protocol Signature Pages
- Laboratory Documents including CAP and CLIA certificates, Lab Director's CV and Medical License, and Reference Ranges
- Supplies for study conduct, including CRFs, specimen collection and lab materials, and shipping materials
- Site Initiation Visit and Training Log

5.2 Facilities Requirements

5.2.1 Clinical Research Area
The participating local sites will provide adequate clinical areas to conduct the study.

5.2.2 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.

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

5.3 Staff Training

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

5.3.2 Protocol Training
Study staff will receive training on aspects relevant to their role of the protocol by way of the Site Initiation Visit, to include:

- Study Objectives
- Inclusion/Exclusion Criteria
- Protocol Deviations
- Treatment Timelines
- Manufacturing Timelines and Logistics
- Subject Visit Schedule
- Screening, Treatment, and End of Study Visits
- Laboratory Evaluations

- Safety Monitoring and Stopping Rules
- Treatment Interruptions or Discontinuation
- 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

SECTION 6: PROTOCOL IMPLEMENTATION

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 may begin once a site is activated and 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 clinicaltrials.gov and the PTCTC website.

6.1.2 Screening
Patients will be identified at the participating institutions. Patients with a diagnosis of AML as defined in the Eligibility criteria who are believed to be potentially eligible by the site investigator will be approached for enrollment.

6.1.3 Establishing Eligibility
See protocol for full details.

6.1.4 Assigning Study Identification Numbers (Study ID)
Potential recipients will be assigned a Study ID Number when sites inform the coordinating center of a potential new patient. This number will consist of the three-letter/four-number study identifier (CEL2001), a site identifier (e.g., NCH for Nationwide Children's Hospital, CHLA for Children's Hospital Los Angeles), a two-digit number, and the letter "R".

The two-digit terminal portion of the Study ID will be serially assigned independently for each site (e.g., CEL2001-NCH-01-R, CEL2001-JHU-01-R). This number will remain with this patient throughout their participation in this study. Some study ID numbers may be assigned for patients that ultimately do not meet eligibility to be enrolled on the study.

After determining eligibility and consenting the donor, a corresponding study ID Number will be assigned with the letter "D" (e.g., CEL2001-NCH-01-D, CEL2001-JHU-01-D, etc.).

6.1.5 Enrollment Procedures
Pre-transplant recipient workup and protocol consent documents will be signed per local institutional practices. 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. Donor workup and signed consent must be obtained prior to collection of

donor peripheral blood.

- Patient is identified as a potential study candidate by their local transplant physician.
- Site study personnel contact the PTCTC Coordinating Center (EXCEL@chla.usc.edu) to inform of possible new patient as early as possible.
- Once a site is ready to commit to manufacturing dates, formal request must be submitted via EXCEL Enrollment Request Form (see Appendix XI).
- PTCTC Coordinating Center notifies EXCEL study leadership to confirm enrollment spot is available. Please refer to protocol section 5.4 for additional details on enrollment.
- PTCTC Coordinating Center assigns a study ID and coordinates with the local clinical site and manufacturing site (Nationwide Children's Hospital) to confirm manufacturing dates (see Section 7.1).
- When manufacturing dates are confirmed, local study site completes donor workup, establishes donor eligibility, and donor signs the informed consent document.
- When donor eligibility is confirmed and consents are signed, the local study site collects the donor peripheral blood for NK cell manufacturing and ships the blood to manufacturing site.
- When patient eligibility is confirmed by the local transplant physician, the patient or patient's parent/guardian(s) signs the study treatment permission form, and site study personnel complete the Recipient Demographics and Eligibility eCRFs in Medidata Rave and upload any required and/or relevant diagnostic documentation.
- Study site personnel notify PTCTC Coordinating Center (EXCEL@chla.usc.edu) of completed eCRFs.
- PTCTC Coordinating Center confirms eligibility and communicates formal patient enrollment and enrollment date to site.

Section 7: Detailed Description of Study Procedures

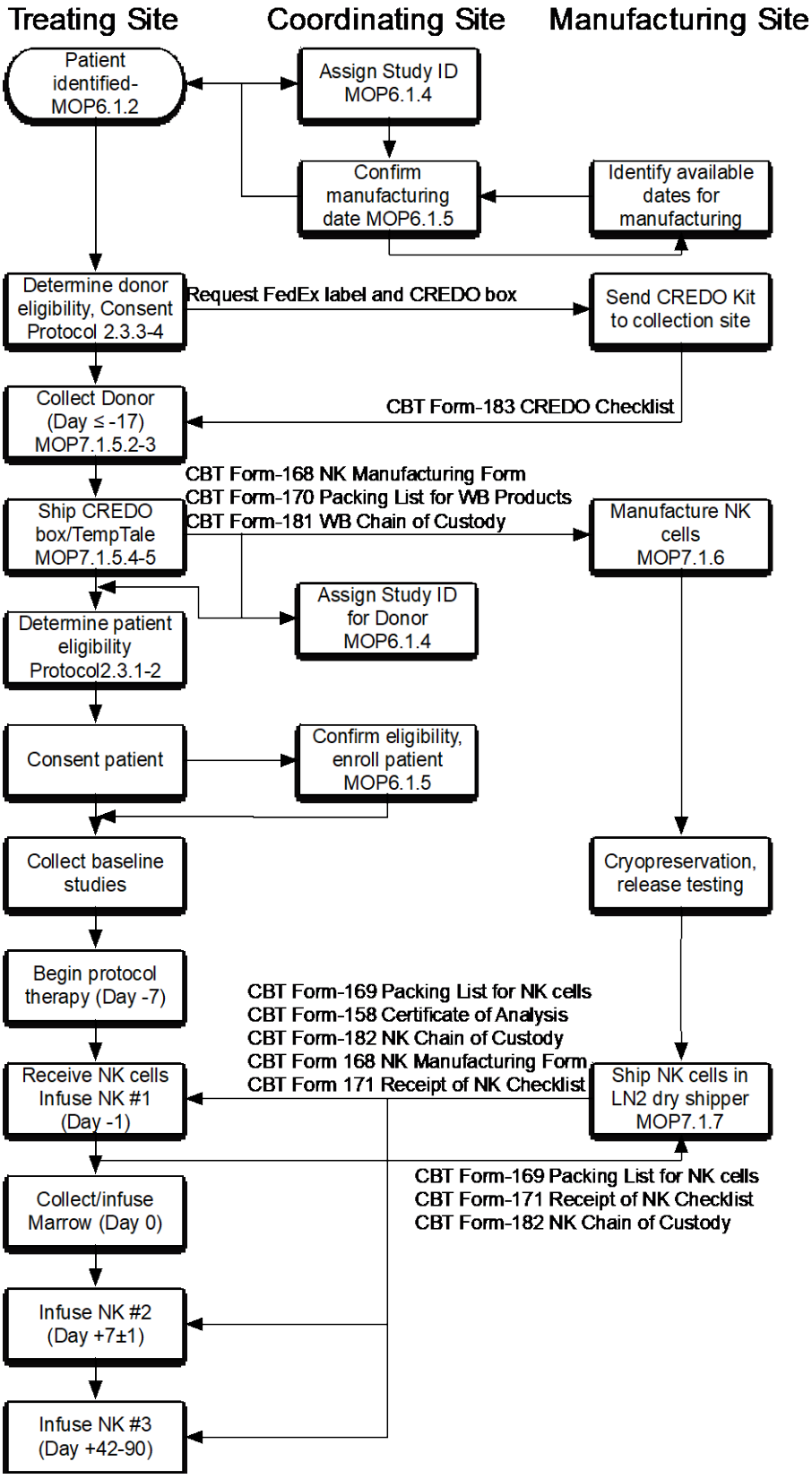
See protocol for full details.

7.1 NK Cell Product Manufacturing:

7.1.1 Key Personnel and Contact Information

Name	Role	Email	Phone
CHLA PTCTC Operations Center	All EXCEL Study Communications	EXCEL@chla.usc.edu	
Shane Wellman	CBT Business Manager	Shane.Wellman@nationwidechildrens.org	614-355-3598
Dean Lee	Scientific Director	Dean.Lee @nationwidechildrens.org	(614) 355-3594

7.1.2 Flow Chart Overview



7.1.3 Patient Enrollment, Scheduling and Donor Blood Collection

7.1.3.1 Manufacturing Request

Pre-collection activities:

- Central Study Coordinator confirms cell therapy lab/pharmacy addresses/contact information of the local clinical site
- Potential manufacturing dates are identified by CBT Core NCH and a date is selected by the Central Study Coordinator
- Complete NK Cell Manufacturing Form (CBT-FORM 168-01) with Site and Patient (Recipient) information requesting Physician's signature.

7.1.3.2 Recommended Initial Blood Collection

There are two methods that have been tested for donor blood collection with heparin anticoagulant and outlined below: the push-pull method and the scale method. Centers can choose which method they prefer to use and adopt using their own Center's standard operating procedures. ***Citrate anticoagulant is not allowed.***

Note: Alternative collection methods that substantially deviate from these two examples are allowed only if reviewed and approved by the EXCEL study committee in advance of collection.

7.1.3.2.1 Push-Pull Method

This method is most easily transportable to sites but requires a longer collection time and may require a more stable peripheral IV due to length of procedure. There is a higher chance that the peripheral IV may need to be replaced as a result, compared to the scale method below. At most sites that do not have easy access to a Blood Bank collection site or Apheresis Unit, the push-pull method may be easier to implement.

Materials:

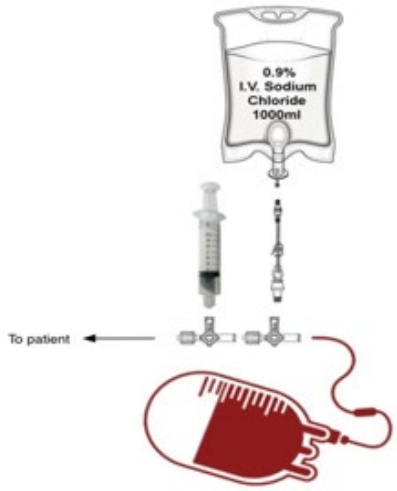
- Two 3-way stopcocks (2 female luer locks and 1 male luer lock)
- Sterile 600 cc blood collection bag
- Preservative-free sodium heparin (1000 units/ mL) – see Table 2 below for heparin volume
- Each vial holds 2 mL
- One 10mL syringe for blood collection
- One 5mL syringe sodium heparin
- (Optional) 500mL Normal Saline (NS) bag and tubing for administration of NS if needed (for example, if donor requires extra fluid for clinical reasons during blood collection*)

Procedure:

- Place peripheral IV
- Maintain a sterile surface as you unwrap the materials from their packaging
- Keep ends of the 3-way stopcocks sterile as you connect them to peripheral IV

- Load empty 5mL syringe with required sodium heparin and connect to 3-way stopcock (**Figure 2**)
- Attach the 600mL collection bag to the end of the apparatus
- Connect apparatus to peripheral IV
- Flush sodium heparin into collection bag <u>sufficient for total blood collection</u> (10 Units/mL, e.g., 4500 Units (4.5mL of 1000 U/mL))
- Collect blood into 10mL syringe and transfer to collection bag
- Repeat until full <u>450mL</u> blood volume (or lesser weight-based volume) is collected
- Complete NK Cell Manufacturing Form (CBT-FORM 168-01)

Figure 2 – Setup with optional saline



***NOTE:** If anytime during the initial blood collection procedure patient is symptomatic (hypotension, dizziness, has a headache, weakness or fainting), stop procedure, disconnect sodium heparin syringe, attach 500mL Normal Saline (NS) bag/tubing and infuse 10mL/kg of NS (**Figure 2**).*

7.1.3.2.2 Scale Method

The scale method is faster and requires less nursing time but requires prior validation and special training/expertise. This is the method typically used by Blood Banks and Apheresis Centers for collection of volunteer peripheral blood and may already be set up at your Center. The scale that is used must be previously validated to be used for blood collection.

Materials:

- ChloraPrep®, One-Step Frepp Applicators
- Povidone-Iodine Duo-swab, for alternate donor arm scrub
- 600 mL RBC Collection bag **(no anticoagulant)** e.g. Terumo T-150 Teruflex transfer bags (product number 1BB-D606A)
- Blood Scale with Shaker
- Preservative-free sodium heparin (1000 units/ mL) – see Table 2 below for heparin volume

Procedure:

<u>Prepare Collection Bag</u>

- Take a 600 mL whole blood collection bag without any anticoagulant.
    - Using aseptic techniques add a phlebotomy needle (if needed) and remove any unnecessary tubing if attached to the bag.
    - If the collection bag does not have an injection port, using aseptic techniques weld (connect) an injection port to the collection bag. .
    - Some collection bags do not have the capacity to weld (attach) a sampling pouch/port. In that case, it is appropriate to spike the bag to add the heparin solution.

- Based on the total volume of whole blood to be collected, order required units of preservative-free heparin from pharmacy (Table 2 below). Most cases will be adding 4500 U of heparin as that is the goal blood collection.
- Using aseptic techniques, inject heparinized saline into the collection bag using the injection port or by spiking the bag
    - Consider diluting the heparin in 30-60mL NS to allow proper coating of bag and mixing with the whole blood
- Gently rock bag back and forth for about 1 minute to coat the surface of the bag with heparin NS mixture prior to collection of whole blood.
- Tare prepared heparin collection bag on scale to collect the desired amount of blood (1 ml Whole Blood=1.06 grams. Example, for 450 mL target collection should aim for 477 gms of whole blood).
- Follow proper arm scrub steps and other site-specific steps to prepare donor for Whole Blood Phlebotomy.
- Using aseptic techniques perform phlebotomy on the donor.
- Stop phlebotomy when desired volume of whole blood has been collected.

Table 2: Heparin Volume

Weight of Recipient (kg)	**Total <u>Minimum</u> Donor Blood Collection (mL)**	**Final Sodium Heparin Concentration-Required (Units/mL)**	**Sodium Heparin (units) Required**	**Sodium Heparin (mL) Required**	**# Sodium Heparin vials (2 mL/vial)**
≤ 20	200	10	2000	2	1
21 - 30	300	10	3000	3	1
31 - 40	400	10	4000	4	2
≥ 41	450	10	4500	4.5	2

NOTE: Extra heparin in the collection bag will not harm the product. For example, the goal collection for every donor is 450 mL of peripheral blood. Therefore, the donor's collection bag will be set up in advance with 4500 Units of heparin. If the recipient weighs 30 kg, the minimum acceptable volume of donor blood to collect is 300 mL (10 mL/kg of recipient weight, to a max of 450 mL). If the 450 mL collection cannot be completed (inability to replace lost IV etc.) but a minimum of 300 mL of donor blood (with 4500 U of heparin) has been collected, it is acceptable to end the collection.

NOTE: As part of donor screening, the ability to collect via peripheral IV should be confirmed*. If this is not possible and there is another equally suitable donor based on the donor selection algorithm as outlined in the protocol (**Section 2.3.5**) another donor could be considered. However, should the original donor be deemed the best based on algorithm, the donor will be consented to undergo a temporary central line placement for peripheral blood collection. This should be a very rare scenario and decision-making will be determined by local PI in consultation with the Protocol Chairs.*

7.1.3.3 Collection Label

An ISBT128-compliant labeling system should be used. If needed, this may be achieved using the Word template provided as Exhibit X, which incorporates the following information on a standard 1.75"x3" label:

- Assigned DIN
- Product type and Code, Division – (NC, Whole Blood, S1284, A0, B0, etc.)
- Collection Date/ Time and Time Zone
- Patient (Donor) name, MRN, and DOB
- Study ID# (CEL2001-SITE-XX-D)

If a DIN is not assigned at the collecting site, it will be assigned by the manufacturing center. Sample:

DIN Label

Name: John Doe

MRN: 123456789

DOB: 1/1/1111

Collection Date: ___/___/_____
MON / DAY / YEAR

PTCTC STUDY ID#: CEL2001-SiteID-XX

Collection Time (time zone): ____:_____ - _____ (indicate daylight/standard (e.g., EST vs EDT)

NC, WHOLE BLOOD S1284

Volume _____ mL

in 15U/mL Heparin

Store at 18-25

Please note that the name and PTCTC Study ID refer to the DONOR from whom this blood was collected.

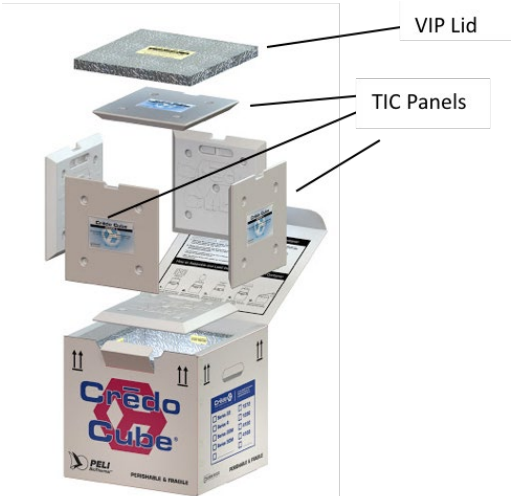
7.1.3.4 Preparation of the Credo Cube

A blood product shipping package (Credo Cube C4-496, TempTale™ Ultra temperature monitoring device, and checklist) will be provided by NCH CBT Core once the manufacturing calendar is confirmed (**Figure 4**).

Materials Included:

- The Credo Cube shipping box
- 6 Thermal Isolation Chamber (TIC) panels
- 1 Vacuum Insulation Panel (VIP) Lid
- TempTale™ Ultra Temperature Monitoring device
- Aqui-Pak™ Absorbent Pouches, 6 bays (Therapak Cat#10316) or equivalent
- Liquid-tight Zip-style or sealable specimen bag
- Fisherbrand™ Universal All-Purpose Absorbent Pads (Fisher Cat# 19-40-910 or equivalent)
- Sufficient Package cushioning, such as bubble wrap, air pillows, absorbent lab pads, egg crate or packing foam to fill CREDO Cube.

Figure 4.



The Credo Cube shipping box

Forms needed:

- **CBT-Form-168** NK Cell Manufacturing Form
- **CBT-Form-181** Whole Blood Product Chain of Custody
- **CBT-Form-170** Packing List for Whole Blood Products
- **CBT-Form-183** Credo Cube Conditioning, Assembly and Shipping Checklist

Do not include any other site-specific documents. Only the approved EXCEL study documents listed should be inserted when returning the Credo Cube shipping box.

Credo Cube Conditioning: Credo Cube preparation MUST begin >24hrs BEFORE loading.

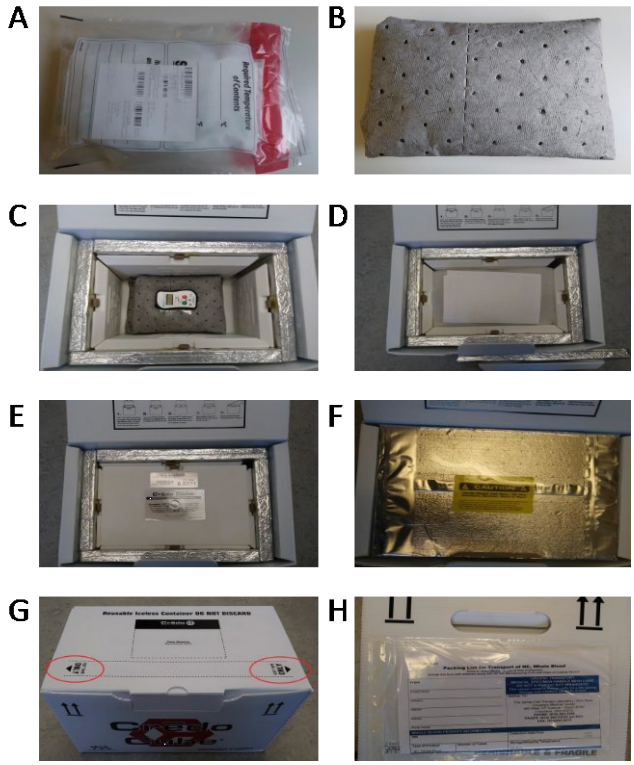
- All 6 TIC panels are to be stored at ambient room temperature for over 24 hours to ensure proper panel conditioning. The panels must be stored with the coolant side (larger side) facing down. Panels must be stored in stacks no more than two panels high. A diagram of the desired storage configuration is shown in **Figure 5**.

Figure 5

Credo Cube Packing (**Figure 6**)

- Complete **CBT-Form-170** Packing List for Transport of Whole Blood
- Check the expiration date on the side of the TempTale™ device and on the inside IP lid of the CREDO shipper. DO NOT USE if it is past the expiration date. Record/confirm the serial number and expiration date on **CBT-Form-170**.
- Insert collection bag at ambient room temperature inside the liquid-tight secondary bag (**Figure 6A**).
- Tightly wrap the bag in a universal absorbent material (**Figure 6B**).
- Activate the TempTale™ device by pressing and holding the Start button (1-3 seconds) until the "sunshine" icon appears in the upper left corner of the display. Remove the adhesive strip from the back of the TempTale™ and affix the TempTale™ device face up on the universal absorbent material covering the blood bag (**Figure 6C**).
- Place bag in the CREDO Cube. Ensure the bag is surrounded by package cushioning.
- Place **CBT-Form-168** NK Cell Manufacturing Form, then the top TIC panel, and then the VIC lid on top of the packaging materials (**Figure 6, D-F**).
- Seal CREDO Cube with packing tape where indicated on the outside box (**Figure 6G**).

Figure 6.



- Affix **CBT-Form-170** Packing List and **CBT-Form-181** Chain of Custody to top of Credo Package (**Figure 6H**).

7.1.4 Blood Product Shipping

- Print and attached FedEx shipping label
- Arrange for FedEx pickup by calling 1-800-463-3339:
    1) Select "schedule a pickup"
    2) Select "schedule a pickup using a label"
    3) Enter tracking number from label
    4) Arrange for pickup at specific location (be sure to specify a room number or address separate from FedEx box location) and time.

NOTE: Product must be directly released to a FedEx employee. At no time shall the product be left unattended in an unsecure location (e.g. FedEx drop off location).

- Send email notification of FedEx shipment with tracking information to:
    - EXCEL@chla.usc.edu;
    - Shane.Wellman@nationwidechildrens.org;
    - Dean.Lee@nationwidechildrens.org;

7.1.5 Blood Product Receipt and Manufacturing

- CBT staff will accept the Whole Blood Product from FedEx and complete:
    - **CBT-Form-185** Receipt of Whole Blood Product Checklist
    - **CBT-Form-170** Packing List for Whole Blood Products
    - **CBT-Form-181** Whole Blood Product Chain of Custody
- NK Manufacturing will be initiated upon receipt according to CMC

7.1.5.1 Notification procedure for Out of Specification (OOS) results

If at any point during the NK cell manufacturing process an OOS result, *i.e*. contamination, is found to occur, the NCH Cell-Based Therapy (CBT) Core will immediately notify the site principal investigator 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 peripheral blood used generating the NK cells is found to be contaminated, possibly during collection, the NCH CBT Core will also inform 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 NK cell product are filed with the processing records and kept according to SOPs. Collection 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.

If NK cell products have already been infused at the time of notification, the treating physician, in consultation with the CBT Medical Director as appropriate, will determine the need for monitoring of the patient, follow up cultures, and treatment as clinically indicated. For NK cell products that have not been infused, the treating physician, in consultation with the CBT Medical Director as appropriate, will determine relative risk to the patient and if infusion is warranted, the monitoring of the patient, follow up cultures, and treatment plan.

7.1.6 NK Cell Product Delivery for Infusion

Once release testing is completed, the product label is completed, and all products will be shipped

from NCH CBT Core to the transplant center in a validated transport container.

Forms included:
  - **CBT-Form-169** Packing List for NK Cells
  - **CBT-Form-171** Receipt of Final NK Cell Product Checklist
  - **CBT-Form-182** NK Cell Product Chain of Custody
  - **CBT-Form-158** Cryopreserved NK Cell Certificate of Analysis
- The cryopreserved NK Cell product will be shipped from the CBT Core NCH to the infusion site by World Courier. A certified, validated and temperature-monitored LN2 dry shipper will be used. Once the Manufactured NK Cell Product is in route, CBT Core NCH will send an email notification containing Tracking information to:
  - EXCEL@chla.usc.edu
  - Relevant study site coordinators
  - Local cell therapy lab (and/or investigational pharmacy contacts, if applicable)
- Receiving site will fill out the following documents and email scanned copies of the completed forms to Shane.Wellman@nationwidechildrens.org:
  - **CBT-Form-169** Packing List for NK Cells
  - **CBT-Form-171** Receipt of Final NK Cell Product Checklist
  - **CBT-Form-182** NK Cell Product Chain of Custody
- Manufactured NK Cell Product should be stored at <-150°C (liquid nitrogen) in an environment controlled by the cell therapy lab/investigational pharmacy until use (See Appendix XV, Form 171-01).
- Prior to infusion, the NK Cell Product should be delivered to the bedside in liquid nitrogen, dry ice, or similar temperature-controlled transport container for cellular therapies according to the local clinical site's standard practice.
- 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.
- The NK Cell Product should be thawed in a water bath, plasma thawer, or similar thawing device intended for cell therapy products according to the clinical site's standard practice.
- The NK Cell Product should be infused within 30 minutes of thawing, preferably using a tubing set that incorporates a 70 micron filter, but should be infused according to the clinical site's standard practice for therapeutic cells (e.g., SOP for CAR-T cells or DLI if there is no NK-specific SOP)).
- Infusion information (date and times, identity of infusion team member, any adverse events associated with infusion, etc.) must be recorded on forms as provided by the sites cell therapy laboratory/pharmacy, or in the electronic chart record, according to the site's standard practice for infusion documentation.

7.2 Specimens and Laboratory Management

7.2.1 Standard Clinical Care Studies

Standard clinical care studies on this protocol will be performed locally (as detailed in the protocol) and will include

- CBC and differential
- Busulfan pharmacokinetics
- Phenotypic characteristics of graft

For information regarding the schedule of standard clinical care studies, please see protocol Section 3.2 and 3.3. Results of these studies will be reported in Medidata Rave.

7.2.2 Research Specimen Collection for Correlative Studies

Research studies on this protocol will be centralized. Samples should be obtained using institutional SOPs.

7.2.3 Sample Processing

PB samples (10 ml in Sodium Heparin or Lithium Heparin tube at ambient temperature) will be collected at Days +14 (± 3), +42 (± 14), +56 (± 14), +100 (± 30).

7.2.3 Sample Labeling

Specimen labels should include the following information:

- Study ID number:
- Patient's Study ID (CEL2001-SITE-XX-R)
- Specimen identifier
- Protocol sampling time point (i.e. days post-transplant)
- Date and time of blood draw.

7.2.4 Sample Shipping

Samples should be shipped on Mondays – Thursdays to allow for weekday delivery and should be shipped the same day they are obtained whenever feasible.

The samples should be shipped in a Styrofoam container with at least one 8 oz room-temperature Gel-Pack or equivalent, via Federal Express Priority Overnight Delivery to the following address:

Company:	Nationwide Children's Hospital Research Institute
Contact Name:	Robin Nakkula
Address 1:	700 Children's Dr WA 4112
Address 2:	Dean Lee Lab
City/State/ZIP:	Columbus, Ohio 43205
Phone No.:	614-355-1538
Email:	Robin.Nakkula@nationwidechildrens.org
FedEx account number:	**6429-2739-6**

Section 8: DATA MANAGEMENT

8.1 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.

8.2 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 3.12 Document Maintenance.

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.

8.3 Source Documentation Requirements

The source document is defined as the first place the data are recorded.
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.

8.4 Study Forms

Case Report Forms (CRFs) will be produced by the Data Manager in Medidata Rave. Access to Medidata Rave will be granted to trained and qualified staff and investigators at local sites.

8.5 Case Report Form Completion Guidelines

Data should be transcribed from source documentation into the Medidata Rave system as soon as possible, but preferably within one calendar week to ensure accuracy.

Study Form Submission Timeframes

Form in Medidata Rave	Submission Timeframe
Recipient Registration and Demographics	At least 2 weeks prior to the start of conditioning
Donor Screening	Prior to first infusion date
Recipient Inclusion/Exclusion Criteria	At least 1 week prior to the start of conditioning
Time-specific CRFs • Day +100 • Day +180 • 1 year • 2 year	Within 30 days of the study timepoint
Adverse Event (Please refer to Tables 1 and 2 of Appendix XII)	SAEs: within 3-7 business days of knowledge of the event as applicable AESIs: within 3 business days of knowledge of the event Grade 3-4 unexpected AEs: within 7 (if unrelated) and 3 (if related) business days of PI knowledge of the event.
Protocol Deviation	Within 7 business days of PI knowledge of the event
Termination	Within 7 business days of PI knowledge of the event
Death	Within 7 business days of PI knowledge of the event
Off-Study	Within 7 business days of study exit event date

8.6 Data Review

The PTCTC staff will review the data forms received from the sites for completeness, internal consistency, protocol compliance and adherence to the protocol. The PTCTC 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.

8.7 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.

8.8 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 PTCTC 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 to ascertain whether an entry should be queried.

8.9 Data Management Reports

PTCTC 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.

8.10 Data Quality Management

The PTCTC 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 PTCTC Coordinating Center, to include the Protocol Officer.

Weekly, the PTCTC 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 PTCTC Project Manager will prepare a report including tabular summaries of all SAEs and deaths on study to date. The report will also

include a summary of each previously unreported SAE and death, including an assessment of whether the event was unexpected or related to the study.

8.11 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.

8.12 Long Term Storage of Case Report Forms

See MOP Document Maintenance in section 3.12.

8.13 Maintaining Data Privacy

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

SECTION 9: 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
- The conduct of the trial is in compliance with the currently approved protocol/amendment (s), with GCP, and with applicable regulatory requirements

9.1 Monitor Responsibilities

Monitoring may be performed by a qualified member of the PTCTC CHLA auditing/monitoring team. While the primary purpose of monitoring is ensuring protocol compliance, monitoring visits also provide a venue for information exchange between the PTCTC Coordinating Center 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.

9.2 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, and the Protocol Officer. 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

9.3 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 Medical Monitor and Protocol Chairs.

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 Protocol Chair, and the Medical Monitor. Serious violations will be reported to the PTCTC Chair. The PTCTC Coordinating Center 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.

9.4 Site Initiation Visits

This study will require a specific site initiation visit (SIV) to be performed. SIV activities will be performed by PTCTC staff for each center once all regulatory and contractual paperwork has been completed, but before any subjects have been enrolled at that site. The SIV will cover the training topics described in 5.3.2, focusing on the following areas:

- Detailed discussion of the protocol
- Drug Accountability and Administration (e.g., NK cell product collection, packaging, shipping, receipt, storage, infusion, and chain of custody)
- Adverse Event Reporting
- Case report form completion
- Research sample shipping
- Monitoring visits
- Regulatory Requirements
- Any other items of importance

SIVs can be performed in person or remotely via web-based training system. At a minimum, site PI, lead study coordinator, donor blood collection personnel (i.e., apheresis team or infusion nurse depending on site), and group at your center who will accept the final NK cell cryopreserved

products (i.e., cell therapy or investigational pharmacy depending on site) **have mandatory attendance** for the in person or remote SIV in order to officially activate a center. Co/Sub-Investigators and back up study coordinators are optional attendees but must self-train and document their training on the EXCEL Training Log.

9.5 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

9.6 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 PTCTC Coordinator and Chair will be notified. The Protocol Chair, PTCTC 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 PTCTC Chair or Executive Committee for discussion of site management.

9.7 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.

9.8 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 site's accrual and timing of the previous monitoring visit.

9.9 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.

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

9.11 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 PTCTC Coordinating Center to analyze and review site performance. The PTCTC 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 PTCTC Coordinating Center and provided to participating sites, the protocol team, and the PTCTC Chair. Centers not meeting accrual goals will be reviewed by the PTCTC Chair, the Protocol Officer, and/or the Protocol Chair to determine the cause of slow accrual and if any corrective processes would improve accrual.

The Protocol Coordinator and/or PTCTC 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 of the Medical Monitor, who has the option to deal directly with the issue for minor concerns or refer to the PTCTC Chair or Executive Committee for discussion of site management. The PTCTC 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.

SECTION 10: STUDY COMPLETION AND CLOSE-OUT PROCEDURES

10.1 Participant Notification

Participants will not be notified in any way.

10.2 Site Procedures

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.

10.3 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 anticipated 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

10.4 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 outcome of data analysis.

10.5 Long Term Storage of Study Documentation

See MOP **Section 3.12** Document Maintenance.

SECTION 11: APPENDICES

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	Federal Wide 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
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

Appendix II: Whole Blood Product Chain of Custody (Form 181-01)

3 PAGES

Appendix III: NK Cell Manufacturing Form (Form 168-01)

1 PAGE

Appendix IV: Packing List for Whole Blood Products (Form 170-01)

1 PAGE

Appendix V: Credo Cube Panel Conditioning, Assembly, and Shipping Checklist (Form 183-01)

3 PAGES

Appendix VI: Expanded NK Cell Certificate of Analysis (Form 158-02)

2 PAGES

Appendix VII: NK Cell Product Chain of Custody (Form 182-01)

3 PAGES

Appendix VIII: Packing List for NK Cells (Form 169-01)

1 PAGE

Appendix IX: Receipt of Final NK Cell Product Checklist (Form 171-01)

1 PAGE

Appendix X: PTCTC CEL2001 (EXCEL) Collection Label Template

1 PAGE

Appendix XI: EXCEL Enrollment Request Form

1 PAGE

Appendix XII: Adverse Event Reporting Tables
2 Pages