INDIANA UNIVERSITY
MELVIN AND BREN SIMON
COMPREHENSIVE CANCER CENTER

CONFIDENTIAL

Cell Therapy Manual

CTO-IUSCCC-ICG122-101

A Phase I, Multicenter Study of CD4- directed chimeric antigen receptor engineered T-cells (CD4CAR) in patients with Relapsed or Refractory CD4+ Lymphoid Hematological Malignancies

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Coordinating Center:
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

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1.0 GENERAL INFORMATION

1.1 Overview of Manual

This Cell Therapy Manual complements protocol CTO-IUSCCC-ICG122-101 by providing additional information on how the cell therapy aspects of the study should be conducted to ensure compliance with the protocol, the principles of Good Clinical Practice (GCP), the International Conference on Harmonization (ICH) guidelines, and Indiana University Melvin and Bren Simon Comprehensive Cancer Center (IUSCCC) Clinical Trials Office's (CTO) requirements.

All individuals who are responsible for conducting Protocol CTO-IUSCCC-ICG122-101 should refer to this manual in conjunction with the protocol.

1.2 Study Roles and Responsibilities

- Huda Salman, MD is the Sponsor-Investigator of this clinical study and is responsible for providing coverage to evaluate eligibility questions, answering safety related questions, and reviewing serious adverse event (SAE) reports.
- The Indiana University Melvin and Bren Simon Comprehensive Cancer Center (IUSCCC) Clinical Trials Office (CTO) is responsible for clinical trial management, serious adverse event (SAE) management and sponsor-investigator communications.
- The IUSCCC's Multicenter Project Manager (MPM) is the participating sites' first line of communication. The MPM is responsible for clinical trial oversight, receipt and evaluation of SAE reports from participating study sites, ensuring protocol compliance to ICH-GCP, local and federal regulations
- The respective local institutional review boards (IRBs) will be used during this study to grant approval for research conduct at each center.
- This study will be conducted in accordance with the protocol and all local and federal regulations including ICH-GCP, and IUSCCC standard operating procedures.

1.3 Contact Information

Study Representative	Contact
Sponsor- Investigator	Huda Salman, MD Telephone: (317) 278-9504 E-mail: hsalman@iu.edu
Multicenter Project Manager	Sheri Jones Telephone: (317) 278-5165 E-mail: srlipps@iu.edu Fax: (317) 274-8022
Director of Cell and Gene Therapy Manufacturing	Emily Hopewell, PhD Phone: (317) 278-1109 E-mail: emlhope@iu.edu
Director Cell Immunotherapy and Transduction (GMP Facility)	Vicki Graves Phone: (317) 274-5732 E-mail: vlgraves@iu.edu vlgraves@iu.edu
Manager of Apheresis and Cellular Therapy Laboratory	Dave Schwering 317-944-2558 Office dschwering@IUHealth.org

2.0 STUDY SUPPLIES AND MATERIALS

Each institution will be responsible for procuring supplies necessary for administration of IP unless otherwise specified.

2.1 Investigational Product (IP): CD4CAR T-cells

How Supplied: One to two 10-30mL cryobags

2.2 Supplies for Infusion of IP

- Refer to section 9.2.2 in the protocol for a complete list

2.3 Labeling

- Collection and product labels must be ISBT 128 compliant

3.0 APHERESIS

Communication must be sent to the MPM at the Coordinating Center at least 14 days in advance that an Apheresis collection has scheduled; so that they can coordinate with the manufacturing facilities to determine where the cells will be shipped. Apheresis collection should be performed according to site standard operating procedures.

Refer to section 8.3.1.2 of the protocol for more information.

3.1 Transfer of Apheresis Product

IUSCCC: Apheresis product will be received by the Cellular Therapy lab and then transferred to the Cellular Immunotherapy and Transduction lab for manufacturing (or shipping if Louisville will be manufacturing) within one hour of collection end time. If more time is required, please place into appropriate temperature monitored storage (2-8 °C) until the time of transfer occurs. Apheresis product needs to arrive at manufacturing facility within 24 hours of collection.

Participating Sites: Apheresis product will be shipped to the Indiana University Cell Immunotherapy and Transduction Facility or the University of Louisville Dunbar CAR T-Cell GMP Facility. Apheresis product must be transferred and placed into 2-8 °C shipper within one hour (60 minutes) of collection end time. If more time is required, please place into appropriate temperature monitored storage (2-8 °C) until the time of shipment occurs. Shipment needs to arrive at manufacturing facility within 24 hours of collection. Contact the multicenter project manager if these conditions cannot be met.

Complete the Chain of Custody form (or institutional equivalent) in appendix 10.8.

4.0 MANUFACTURING OF IP

Manufacturing of IP will take place at either the Indiana University Cell Immunotherapy and Transduction Facility or the University of Louisville Dunbar CART-Cell GMP Facility.

5.0 CRYOPRESERVATION AND PACKAGING OF IP

Refer to section 8.3.1.3 in the protocol for more information.

At the end of cell culture, the cells are cryopreserved in infusible cryomedia and will be shipped to the site following completion of release testing. Cell products will be stored at or below -150^{o} C in a vapor nitrogen freezer.

6.0 SHIPMENT OF IP

IP (CD4CAR T cells) is manufactured after a subject is enrolled and has completed apheresis. The cell product is expected to be ready for release approximately 4 weeks after apheresis.

IUSCCC: After completion of manufacturing of the CD4CAR cellular product, one bag will be transferred to the Cellular Therapy Lab for temporary storage until the time of infusion. The certificate of analysis form and chain of custody document will accompany IP.

Participating sites: After completion of manufacturing of the CD4CAR cellular product, one bag of CD4CAR T cells will be shipped directly to the site via a temperature monitored liquid nitrogen cryoshipper. All necessary documentation will accompany the shipment. Additional bags of subject specific CD4CAR T cells will remain at the processing facility as back up infusions. The certificate of analysis form and chain of custody document will accompany IP.

The LN2 Dry Shipper will be charged and temperature monitored per institution standard procedures. **NOTE:** Cells shall be transported at or below -150 degrees Celsius in the vapor phase of liquid nitrogen (dry shipper).

Appropriate shipping and warning labels are applied to the outer shipping container. When IP is transported the temperature of the shipper is monitored continuously.

Refer to section 8.3.3 of the protocol for more information.

Complete the Chain of Custody form (or institutional equivalent) in appendix 10.8.

6.1 RECEIPT OF IP

IP will be delivered per section 8.3.4 of the protocol. A chain of custody document will be maintained to document movement of the cells in the facility.

Study staff should verify that the shipment contains all items noted in the shipment inventory included in the shipper. Any damaged or unusable study drug in a shipment should be documented in the study files and reported to the coordinating center immediately.

The following procedures should be followed upon receipt of IP:

- Ensure that the lid of the shipper is sealed upon arrival. Remove the lid (if necessary) and confirm the temperature of the container and record on Cryopreserved Product Receipt Checklist (Appendix 10.6)

- Remove the product from the plastic bag and visually inspect it. Ensure there are no clots and the bag itself is intact. Record the products condition on Cryopreserved Product Receipt Checklist (Appendix 10.6)

- Ensure that all the required documents were sent along with the product.

- The receiving personnel should print and sign their name on Cryopreserved Product Receipt Checklist (Appendix 10.6) and following the emailing instructions on the form

6.2 STORAGE OF IP

Once received by the research site, investigational product must be stored according to the conditions on the label, in a secure location with limited access.

After logging the cells in the research site facility, the bag(s) containing CART-4-transduced T cells will be stored in the research site's Stem Cell Therapy Lab (or equivalent), in a monitored <150°C freezer. Infusion bags will be stored in the freezer until needed. CART-4-transduced T cells will be delivered and stored in accordance with each site's policy.

7.0 IP PREPARATION AND ADMINISTRATION INSTRUCTIONS

7.1 IP Preparation

Refer to section 8.3.5 of the protocol for detailed information.

Complete Appendix 10.3 Investigational Product Thaw Record (or site equivalent).

If the CD4CAR T cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused, and should be returned to the site's cell processing facility. The site coordinator should contact the multicenter project manager immediately to facilitate shipment of back up bag to site. The CD4CAR T cell product expires 6 hours after thaw.

IP preparation must occur based on the time of scheduled administration to account for the 6 hours expiry of the post thawed IP. IP preparation will be performed by appropriately trained staff under the responsibility of the site's Principal Investigator.

7.2 IP Dispensing Labels

A label generated for the thawed IP will include the following at a minimum the following information for the IP Infusion Bag post thaw:

1. Maintain thawed IP at room/ambient temperature and light conditions. Avoid direct sunlight exposure
2. Expiry*:
    a. Preferred format: dd / MON / yyyy HH:MM

*** Expiration time is 6 hours after the IP infusion bag has been thawed**

7.3 IP Administration

Refer to section 9.2.2 in the protocol for detailed instructions.

Prior to Infusion:

On the day of the infusion, the RN will assemble supplies for infusion:

- One 1 liter bag of Plasma-Lyte A injection pH 7.4, one BD Alaris Pump Infusion Burette Set (or equivalent), one secondary admin set with bag hanger, one 10mL syringe, one 20mL syringe, alcohol swabs
- Vital signs cycling every 15 minutes

Below is an example of how the process **could** be performed:

- Open BD Alaris Pump Infusion Burette Set (or equivalent), unwind, and hang on IV pole to prepare to prime set with Plasma-Lyte A. Close all clamps. This will be the primary IV tubing.
- Open secondary admin set. Spike Plasma-Lyte A 1L bag with secondary admin set, ensuring tubing clamp is in the closed position. Attach to luer lock on Buretrol cylinder of primary IV set.
- Prime the Buretol of the BD Alaris Pump Infusion Burette Set (or equivalent)
- Unclamp the primary set below the Buretrol and prime the tubing taking care to avoid getting air in line.
- The Buretrol cylinder should have approximately 15 cc before CAR T-cell products are added.
- Re-clamp the tubing once the priming is complete.
- Spike CAR T- cell bag with the BD Alaris Pump Infusion Burette Set (or equivalent) and add CAR T-cell content to Buretrol cylinder. Clamp tubing from CAR T cell bag to cylinder once contents are infused.

- CAR T-cells are to be diluted with a volume of Plasma-Lyte A, take note to not over-dilute the cells which can cause cellular destruction. The dilution of approximately 15 cc is necessary to increase the volume of the infusion to meet the 20-30 minutes infusion time desired for the first several patients as per protocol.
  Note:
  1. The CAR T-cell volume is estimated at about 10 cc, though may change with increasing doses and manufacturing facility

- This reflects a total of approximately 25 cc in the Buretrol cylinder. Program Alaris pump accordingly to accomplish infusion in 20-30 minutes.

Post Infusion: *Flush (Rinse) and culture*

- Swab additive port of Plasma-Lyte A bag on IV pole with alcohol swab. Puncture diaphragm of port with syringe and needle
- Pull approximately 10 cc Plasma-Lyte A
- Change needle to a vented dispensing pin, or equivalent
- Spike access port of empty CAR T-cell bag with dispensing pin and inject syringe of approximately 10 cc Plasma-Lyte A.
- Massage CAR T- cell bag gently to dispense Plasma-Lyte A
- Unclamp slide clamp and infuse volume into Buretrol cylinder
- Add more Plasma-Lyte A to Buretrol cylinder for an approximate flush of 30 cc.
- Infuse this flush at fast rate, approximately 2 minutes.
- Vital signs, including temperature, respiratory rate, pulse, blood pressure and oxygen saturation will be taken before infusion, every 15 minutes throughout infusion, at completion of infusion and every 15 minutes thereafter for at least one hour until vital signs are satisfactory and stable (may be up to 6 hours post infusion)
- Following infusion and flush, do NOT throw away CAR T-cell bag, Plasma-Lyte A bag or any tubing. Obtain culture specimen from CAR T-cell bag using aseptic technique. The bag will be sent to an institutional clinic for lab cultures, since this is an actionable item if found contaminated
- Label culture bottles with “CAR-T” and the unique product number, and a barcoded patient ID label.

8.0 DESTRUCTION OR RETURN OF INVESTIGATIONAL PRODUCT

Refer to section 8.3.6 in the protocol for further information.

Used or partially used IP and/or IP bags will be destroyed onsite according to site policies and the status should be documented on an On-site IP Inventory Log. IP is considered used once it is thawed.

8.1 IP Return

Refer to section 8.3.6 in the protocol for further information.

8.2 UNDISTRIBUTED IP

Refer to section 8.3.6 in the protocol for further information.

9.0 APPENDICES

Appendix 10.1 CD4CAR T Cell Shipping Memo
Appendix 10.2 CryoShipper Shipping Transport Label
Appendix 10.3 IP Thaw Record
Appendix 10.4 Apheresis Tracking Log
Appendix 10.5 Cell Product Receipt Form
Appendix 10.6 Product Label examples
Appendix 10.7 Chain of Custody Log

9.1 Shipping Memo Form

Shipping facility:
(If you are a participating site, please update with your address)
Apheresis and Cellular Therapy Laboratory
550 N. University Blvd.
Indianapolis, IN 46202
Phone: (317) 948-1400
Contact Person:_____

Product Shipment

Record*Shipper handling instructions:*
Human Cells for Administration
Handle with Care
Do Not X-Ray
Do Not Irradiate

Product DIN	Product Type	Volume (mL)	Collection Date	Packaged Time
Total units = ___				

Product Information
Subject Name: _____
Subject MRN: _____
Subject Date of Birth: _____
Subject Number: _____

Product Type (Select One):

☐**T-Cells, Apheresis**
□Label affixed to product container
□ISBT # is present
□Expiration date and time
□ subject #, DOB
□Volume
□Product placed in secondary sealed plastic “zip lock” bag
□Anticoagulant and volume (if applicable)

☐**MNC, Apheresis**
□Product container is intact
□Collection date and time
□Blood type or N/A
□Product Type

Packaged by:_____

Package verification by:_____

Receiving Facility

Facility _____ Address_____
Contact Person _____Phone # ( ) _____
City, State, Zip_____

Received by:_____
Received time: _____
Received date: _____
Temp at receipt: _____
Data logger alarm: ☐yes ☐no *If yes contact MPM immediately
☐ Data logger scanned and emailed to MPM within 24hours of receipt

****Note: Please use in tandem with 10.8 Chain of Custody Log**

9.2 CryoShipper Shipping Transport Label

LN_2 Dry Shipper Transport Label

Complete information. The distribution time and time zone may be written by hand using black indelible ink. Print full sheet label(s) using qualified label stock and printer. Cut along the dotted line below and attach label to the exterior of the Dry Shipper and the shipping case (if applicable)

✂_ _

Shipper ID or SN:	
Distribution Date:	
Distribution Time:	**Time Zone: EST / EDT/CST/CDT/MST/MDT/PST/PDT (circle one)**
Handling Instructions	**HUMAN CELLS FOR ADMINISTRATION** **HANDLE WITH CARE!** ***DO NOT X-RAY*** ***DO NOT IRRADIATE***
WARNING	**Extremely Cold Contents < -150°C (-238 °F)** **May Cause Severe Frostbite**
Shipping Facility Address	Institution Facility Name Street Address Room Number City State Zip
Shipping Facility Contact	Name: Phone#: Email:
Receiving Facility Address	Institution Facility Name Street Address Room Number City State Zip
Receiving Facility Contact	Name Phone# Email:

DO NOT OPEN THIS SHIPPING CONTAINER UNLESS YOU ARE THE DESIGNATED RECEIVING FACILITY CONTACT OR AUTHORIZED DESIGNEE

Product Transport Label

Qualified Shipping Container ID:	
Distribution Date:	
Distribution Time:	**Time Zone: EST / EDT/CST/CDT/MST/MDT/PST/PDT (circle one)**

MEDICAL SPECIMEN
HANDLE WITH CARE!
DO NOT X-RAY
DO NOT IRRADIATE

Transport Temperature	☐ Ambient ☐ 4° C
Shipping Facility Address	Institution Facility Name Street Address Room Number City State Zip
Shipping Facility Contact	Name: Phone#: Email:
Receiving Facility Address	Institution Facility Name Street Address Room Number City State Zip
Receiving Facility Contact	Name Phone# Email:

9.3 IP Thaw Record

INVESTIGATIONAL PRODUCT THAW RECORD

Study Site:_____

Infusion Date:
Product DIN#:
Subject Study ID:
Water Bath Manufacturer:
Water Bath Serial Number:
Last Calibration Date:
Next Calibration Date:
Temperature Set Point: 37°C

PREPARATION

Disinfect water bath per institution policy Initials:_____

Fill with 0.9% normal saline or sterile water Initials:_____

0.9% Normal Saline Lot#: ☐N/A	Expiration Date: ☐N/A
Sterile Water Lot#: ☐N/A	Expiration Date: ☐N/A

THAW

Record Water Bath Temperature immediately prior to thaw: _____°C

Start Time of Thaw:_____(HH:MM) Time Zone:_____

End Time of Thaw:_____(HH:MM) Time Zone:_____

Product thawed by:_____Initials

Return completed form to Site Coordinator

9.4 Apheresis Tracking Log

Subject Name: _____ Subject #:_____

Subject ISBT#:_____

Date of Apheresis:_____

Apheresis start time:_____ end time:_____

Was the apheresis interrupted due to an adverse event or other reason? (y/n):_____

Apheresis Interruption comments:

Final product volume(mL):_____ Actual total blood volume processed (mL)_____

Concurrent plasma volume (mL):_____ Gram staining result on apheresis product:_____

Comments:

Subject Pre and Post Apheresis Peripheral Testing

Pre Apheresis Date:_____ Time:_____

Test Type	**Results**		**Critical (Circle Yes or No)**
	Pre Apheresis	**Post Apheresis**	
HCT %			Y N (<20%)
WBC ($10^{\wedge 3}$/uL)			Y N
Hgb(g/dL)			Y N
Platelets ($10^{\wedge 3}$/uL)			Y N (<20x$10^{\wedge 3}$/uL)
CD3+ absolute (cell/l)			NA
CD3+ CD4+ CD8-%			
CD3+ CD4+ CD8- absolute			
CD3+ CD8+ CD4- absolute			
CD3+ CD8+ CD4- %			
CD4/CD8 ratio			
CD3+ CD4+ CD8+ %			
CD3+ CD4+ CD8+ absolute			
CD3+ CD4- CD8- %			
CD3+ CD4- CD8- absolute			

Comments:

Analysis:

Apheresis Product Testing date:_____ Time:_____

Test Type	Results
HCT %	
WBC (10^3/uL)	
Hgb(g/dL)	
Platelets (10^3/uL)	
CD3+ absolute (cell/l)	
CD3+ CD4+ CD8-%	
CD3+ CD4+ CD8- absolute	
CD3+ CD8+ CD4- absolute	
CD3+ CD8+ CD4- %	
CD4/CD8 ratio	
CD3+ CD4+ CD8+ %	
CD3+ CD4+ CD8+ absolute	
CD3+ CD4- CD8- %	
CD3+ CD4- CD8- absolute	

Comments:

Completed by:

Signature:_____

Initials:_____

Date:_____

9.5 Cell Product Receipt Form

Cryopreserved Product Receipt Checklist

PRIOR TO SHIPMENT OF PRODUCT				TECH
DIN(s) Assigned: _____				
Subject Name		Sending Institution		
Subject MRN		Product Local ID # (s)		
Subject DOB				
Courier		Scheduled Date/Time of Delivery		

AT PRODUCT RECEIPT					TECH
Canister(s) placed in vapor phase to cool					
Date Received:	Time Received:	Temp. Device ID:	Thermocouple ID:	Omega Temp. of Shipper °C:	
Shipper ID:		Data logger ID:	Data Logger Temp °C:		
Data Logger in alarm at arrival?				□ Yes □ No	
Product Acceptable- Not thawed/cracked				□ Yes □ No	
Sufficient samples provided for required genetic testing or cryovials provided for viability testing?				□ Yes □ No	
Location of product(s) storage and bag type documented below				□ Yes □ No	
Are all required documents present, including but not limited to: · Circular of Information · IDM Test Results · Final Declaration of Eligibility · Microbial Results · Product Insert (Processing Report/Summary)				□ Yes □ No	
Product Receipt form completed and scanned and emailed to sending institution				□ NA	
Institutional BMT Transplant Nursing Coordinator notified of product receipt and required follow-up Person Notified: _____ Notified Via: _____ Date: _____				□ NA	

RECEIPT OF PRODUCTS							
Local Product ID #	**Product ID #(DIN)**	**Bag Type**	**Frame**	**Canister**	**Freezer #**	**Cryovial Location**	**Tech**

Comments: _____
_____
_____

9.6 Product Label Examples

Apheresis Collection Label Example

Final CAR T-Cell Product Label Example

Dispensing label:

Maintain thawed IP at room/ambient temperature and light conditions.

Avoid direct sunlight exposure

Expiry* ___/___/___ ____ ____

Preferred format dd/mon/yyyy HH MM

Expiration time is 6 hours after the IP infusion bag has been thawed

9.7 Chain of Custody Log

CHAIN OF CUSTODY

APHERESIS PRODUCT

Product DIN:		Study # or Acrostic: ☐ N/A		
Shipper to Courier				
Shipper: Shipper Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Courier: Courier Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Courier to Manufacturer				
Courier: Courier Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Manufacturer: Manufacturer Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Please use 24 hour clock and record the time in the time zone in which you are currently located				
Manufacturer Representative: Please scan and e-mail this completed form along with the temperature monitoring file (pdf) to srlipps@iu.edu				

CHAIN OF CUSTODY

INVESTIGATIONAL PRODUCT

Manufacturer to Courier				
Manufacturer: Manufacturer Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Courier: Courier Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Courier to Site of Study Product Administration				
Courier: Courier Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Site of Cellular Product Administration: Representative:	Signature:	Date:	Time:	Time Zone: ☐ EST/EDT ☐CST/CDT ☐MST/MDT ☐PST/PDT
Please use 24 hour clock and record the time in the time zone in which you are currently located				
Infusion Site Representative: Please scan and e-mail the completed form on the day of receipt to srlipps@iu.edu. **Use the enclosed shipping waybill to return the dry shipper as soon as possible**				