20-518 CLINICAL MNC COLLECTION PROTOCOL

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1. PURPOSE

The purpose of this procedure is to define the process for performing and packaging autologous mononuclear cell collections for MGH sponsored clinical trials.

2. SCOPE

This procedure applies to collection centers qualified to perform and package leukapheresis collections for MGH sponsored clinical trials.

3. DEFINITIONS

3.1 Anticoagulant Citrate Dextrose, Formula A (ACD-A)

A chemical substance added to blood that inhibits clotting by binding ionized calcium; for Formula A, each 10ml of solution contains 2.2g sodium citrate hydrous, 730mg citric acid anhydrous and 2.45g dextrose hydrous; also known as sodium citrate.

3.2 Autologous Concurrent Plasma

Subject plasma collected during the mononuclear cell collection and added to the Mononuclear Cell (MNC) Collection Bag. Specific instrument terms used:
Spectra Optia Apheresis System – Plasma

3.3 Chain of Identity

The process that links a subject's autologous blood product to their final product throughout the manufacturing process from the time of the MNC collection through product infusion. Refer to **General Information** section for more information on Chain of Identity.

3.4 Collection Start Time

The clock time when the collection procedure is started; start time for Spectra Optia Apheresis System – when the operator selects **Start Run**.

3.5 Collection End Time

The clock time at the completion of the mononuclear cell collection when no further MNCs are collected. This date and time represents the start of the clock for expiration of the MNC product. For Spectra Optia Apheresis System = end of Rinseback

3.6 Courier Shipping Documentation

Courier shipping label or waybill provided by MGH Clinical team that will be affixed to the top of the MNC shipping container. This documentation may vary depending on the courier who is scheduled to pick up the MNC shipping container.

3.7 Mononuclear Cell (MNC) Bag Label

Label that is affixed to the base label of the collection bag after subject identity verification is performed. The identifiers are verified against the Schedule Confirmation Notification Form and with the subject prior to the collection. This is the first identification step of the manufacturing process to associate the product with an DIN.

3.8 MNC Collection Procedure Record

Document used to record the subject identifiers, subject number, DIN and collection data. This form includes information that will be used to receive the MNC collection at the Dana-Farber manufacturing facility and to manufacture the drug product. A copy of this document must be included with the MNC product in the shipper.

3.9 CMCF-FORM-0546 TriPRIL CAR T Process Order

Document used to formally request DFCI CMCF processing of the apheresis product under protocol 20-518 TriPRIL CAR manufacturing SOP. This document records the subject/recipient identifiers, subject number, MGH MRN, DIN, subject/recipient weight, cell dose level assigned, and anticipated date of infusion.. This form includes information that will be used to receive the MNC collection at the Dana-Farber manufacturing facility and to manufacture the drug product. The CRA will fill outthis document, have PI sign and send just prior to shipment to DFCI CMCF Lab NCT email distribution list (DFCICMCFLabNCT@partners.org) to allow speedy population of their paperwork. An example of the CMCF-FORM-0546 TriPRIL CAR T Process Order is shown in Attachment D.

3.10 Donation Identification Number (DIN)

A unique product specific lot number. The DIN is associated to the subject's autologous blood product from the time of the MNC Collection through product infusion.

3.11 Shipping Address Label

Label that is affixed to the exterior of the MNC shipping container. This label contains the DIN and delivery address of the manufacturing facility. The identifiers are verified with the Schedule Confirmation Notification Form upon receipt of the labels and against the applied MNC Bag label prior to placing the MNC collection into the shipper.

3.12 Mononuclear Cell (MNC) Collection Bag

The bag attached to the MNC procedure tubing kit where collected MNCs are stored. Specific instrument Spectra Optia Apheresis System – Collection Bag.

3.13 Mononuclear Cell (MNC) Product

Final collection configuration consisting of ACD-A, collect volume and 150 mL autologous concurrent plasma. Total product volume should not exceed 450 mL. The product will be sealed using heat seals or metal clips and packaged according to MGH requirements.

3.14 Mononuclear Cell (MNC) Product Expiry

The date and time the MNC collection is no longer viable for further manufacturing. This date and time is a set duration that is based on the Collection End Time.

3.15 Schedule Confirmation Form

MGH issued form containing collection specific identifiers such as: clinical trial protocol, subject number and scheduled collection date.

3.16 Spectra Optia Apheresis System

Automatic blood component separator manufactured by TerumoBCT that uses centrifugation and optical detection (automated interface management system) to perform apheresis procedures. The Spectra Optia Apheresis System is FDA-approved to perform MNC collections.

3.17 Subject Identifiers

Personal identifying information (e.g. name and date of birth) by which an individual can be recognized. Subject identifiers are used with the Subject Number and the DIN to ensure Chain of Identity is maintained.

3.18 Subject Identity Verification

The act of confirming subject identity. This activity is performed by ensuring the subject's identifiers, subject number and DIN on the MNC Bag Label exactly matches the Schedule Confirmation Form. Upon patient arrival, this activity can be performed by either visually confirming the subject's identifiers on the MNC Bag Label exactly matches their identification (e.g. Driver's License or Medical Institution Identification) or by verbally confirming the label content with the subject.

3.19 Subject Number

Clinical trial specific numbering scheme with elements of the clinical protocol, clinical site ID and sequential subject numbering.

3.20 Whole Blood Processed Volume (WBPV)

The amount of subject whole blood that travels over the collect or inlet pump during the collection procedure. For Spectra Optia Apheresis System – Whole Blood Processed Volume. This volume *does not* include anticoagulant.

4. MATERIALS

1. Schedule Confirmation Form
2. CMCF-FORM-0546 TriPRIL CAR T Process Order
3. Mononuclear Cell (MNC) Bag Label
4. MNC Collection Procedure Record
5. Shipping Address Label
6. MNC Shipping Container and packaging materials
    a. NanoCool Long Haul Shipping Unit and Lid
    b. Biohazard Specimen Transport Bag
    c. 12 x 12 inch Absorbent Sheet
    d. Marathon Temperature Data Logger (Model xx)
7. Courier Shipping Documentation
8. ACD-A anticoagulant
9. 0.9% sodium chloride injection (saline) USP
10. Spectra Optia Apheresis System
    Spectra Optia Collection Set (Catalog No. 10120)

5. GENERAL INFORMATION

5.1. Chain of identity

Chain of identity (COI) is the process that links the subject's autologous blood product to the subject from collection through infusion. The process is designed to ensure that the right autologous product gets to the right subject for infusion at the right time. There is no standard analytical testing performed that will identify a mix-up between subject's products, and failure within the COI process could lead to product loss or serious health risk to the subject. The hazards associated with a potential autologous product mix-up necessitates stringent product and quality systems controls to minimize this potential risk.

For the autologous products, the distinct identification code is the Donation Identification Number (DIN). The subject's name, date of birth and the Clinical Subject Number are also used in conjunction with the DIN to ensure the right product is infused into the right subject. The DIN will be maintained through all aspects of the leukapheresis collection, manufacturing, packaging and distribution of product.

When the MNC product is labeled, it is the very first step of the manufacturing process to associate a subject's identifiers with their DIN. There are multiple verification activities throughout the MNC collection process to ensure chain of identity is maintained throughout the collection procedure and shipping process. If these verifications fail at any point of the process, it could create a domino effect and could eventually cause product to be rejected, terminated or infused into the wrong subject, resulting in serious health complications, including death.

5.2 Collections will be held on Mondays or Tuesdays.

5.3 DFCI CMCF should be emailed to confirm a collection slot. Email distribution list is DFCICMCFLABNCT@partners.org.

5.4. The following apheresis instrument and collection programs are approved by MGH for MNC collections:

Spectra Optia Apheresis System - MNC Collection

5.5. Follow institutional policy for the following practices:

1) Safe-handling and personal protection
2) Aseptic technique
3) Subject evaluation and care
4) Venipuncture and Central Venous Access Device (CVAD) use
5) MNC collection except as specifically called out in this policy
6) Biohazard disposal

5.6. ACD-A is the only anticoagulant approved for this procedure.

5.5. Autologous Concurrent Plasma is recommended to be collected at the beginning of the procedure. In the event plasma is not collected at the beginning of the procedure, ensure there is enough time for plasma collection to occur without exceeding the final MNC product volume of 450 mL.150ml of autologous concurrent plasma should be collected.

5.7. No additional material should be added to the MNC Product other than what is specified in this protocol.

5.8. MNC Bag

1) Do not access the access ports on the collect bag.
2) When disconnecting the collection bag, do not strip the collect line.
3) Minimally leave 5 inches of tubing once the collect line is sealed.
4) The MNC Bag may be disconnected and hermetically sealed using a heat sealer or metal clips – do not use knots to tie the collect line.
5) Sterile docking to transfer plasma to the collect bag may be performed on an exception basis – collection center must contact Sponsor to obtain approval.

5.9. Target 12 L whole blood processed for the collection, unless otherwise instructed by the Sponsor. It is ok to process greater than or less than 12 L due to clinical or technical issues; complete as much of the collection as is safe for the subject and ship the product per Packaging and Shipping the MNC Product instructions in Section 8. **NOTE:** The collection volume should not exceed 450 mL and must include 150 mL of autologous concurrent plasma.

5.10. Institutional labeling may be affixed to the base label of the MNC product, if required, but must not obscure the MNC Bag Label.

5.11. Do not sample or test the MNC product.

5.12. Package the MNC product as soon as possible after completing the collection.

5.13. Ship the product at 2-8°C using the Courier's facility supplied MNC shipping container, along with courier documentation. The CRA will email a copy of CMCF-FORM-0546 at DFCICMCFLABNCT@partners.org ahead of actual product shipment to allow pre-population of their paperwork.

5.14. If a deviation to this protocol occurs, report via the *Scheduling & Operations Manual.*

5.15. COLLECTION PARAMETERS

1) Collection procedures should be completed before courier arrival for product pick-up.
2) Whole Blood Processed Volume is the run target for the MNC collection, regardless of apheresis instrument used.
3) MNC Product volume should not exceed 450 mL, including 150 mL autologous concurrent plasma.

4) Spectra Optia Apheresis System
    a) MNC Collection program
    b) WBPV – 12000 mL
    c) Autologous Concurrent Plasma – 150 mL
    d) Inlet:AC Ratio – per manufacturer's recommendation
    e) Collect Flow Rate – per manufacturer's recommendation

6. SUBJECT IDENTITY VERIFICATION

6.1 Receive the Schedule Confirmation Form, Sponsor's MNC Bag Label and Dana-Farber Shipping Address Label. Refer to **Attachment B** and **Attachment C** for an example of the MNC Bag Label and Schedule Confirmation Form.

1) Verify the following information on the Sponsor's MNC Bag Label exactly matches the information on the Schedule Confirmation Form:

a) Subject Study Number

b) Date of Collection

2) If there is a discrepancy, DO NOT proceed. Immediately contact Sponsor for further guidance and to determine if the manual back up label needs to be used.
3) If the MNC Bag Label arrives damaged or is illegible, complete the Manual MNC Bag Label using the Schedule Confirmation Form. Clearly print the subject identifiers (name and date of birth), subject number and DIN onto the Manual MNC Bag Label exactly how it appears on the Schedule Confirmation Form.
4) Verify the following information on the Dana-Farber facility Shipping Address Label exactly matches the information on the Schedule Confirmation Form:
   a) DIN
   b) Delivery Address
5) If there is a discrepancy, DO NOT proceed. Immediately contact Sponsor for further guidance.

6.2. Document the subject's weight on the day of the collection on the MNC Collection Procedure Record. Round the weight to the nearest kilogram (kg). The weight must also be documented on the CMCF-FORM-0546 TriPRIL CAR T Process Orders (attachment D) as this weight will be used for dosing calculations on the final product bags.
NOTE: Subject's weight is used to calculate product dosing. This information must be accurate and current.

6.3. In the presence of the subject, perform subject identity verification. Subject identifiers (Subject's Name) and Subject Study number and DIN on the MNC Bag Label should exactly match the method of subject identity verification being performed:
a) Subject's government issued photo identification,
b) Subject's medical institution identification, or
c) Verbally confirm with the subject that their identifiers on the MNC Bag Label is accurate.

6.4. If there is a discrepancy, DO NOT proceed. Immediately contact Sponsor for further guidance.

6.5. Document the method of subject identity verification on the MNC Collection Procedure Record along with the operator who performed the verification and date and time the verification took place.

7. SPECTRA OPTIA MNC COLLECTION

7.1. Set up Optia for an MNC collection procedure following the Spectra Optia Apheresis System MNC Collection Procedure Guide.
1) Select the MNC procedure.
2) Load and prime the disposable tubing set.

7.2. Configure procedure parameters.

1) Program Whole Blood Processed to 12000 mL.
2) Program plasma collection into the collection bag to 150 mL.
3) Program remaining target values following institutional policy.

NOTE: Do not exceed Collection Parameters as listed above in General Information and Collection Parameters sections.

7.3. Affix verified MNC Bag Label to the MNC collection bag.

7.4. Connect the subject to the tubing set.

7.5. Start the collection.

Record the clock time on the MNC Collection Procedure Record when **Start Run** is selected – this is the Collection Start Time.

7.6. Monitor the Collection

1) Follow institutional policy and the Spectra Optia Apheresis System MNC Collection Procedure Guide for collection performance and procedure optimization.
2) The MNC Product volume should not exceed 450 mL, including 150 mL autologous concurrent plasma.
3) If the Optia System displays the warning that the run target will be attained before the next collection phase, continue blood processing in order to collect the full chamber, then end the collection.
4) If the procedure must be ended early, attempt to collect the contents of a partially full chamber.

7.7. End the Collection

1) When the WBP target is attained, the Run Targets Screen is displayed.
2) Follow the screen prompts to initiate Rinseback sequence.

If autologous plasma was collected to a separate bag, transfer plasma to the collect bag at this time.

3) Record the clock time on the MNC Collection Procedure Record when **Rinseback** is selected – this is the Collection End Time and starts the clock for the expiration of the MNC product.

7.8. Record final run values on the MNC Collection Procedure Record; calculate MNC collection bag volumes.

7.9. Disconnect the MNC Collection Bag from the tubing set.

1) Do not strip the collect line.
2) Position and close the clamps at the top of the collect / sampling lines.
3) Seal the collect line and sampling bulb assembly just above the manifold (**Figure 1**).
4) Leave a minimum of 2 seals or 2 metal clips to seal the collect line.

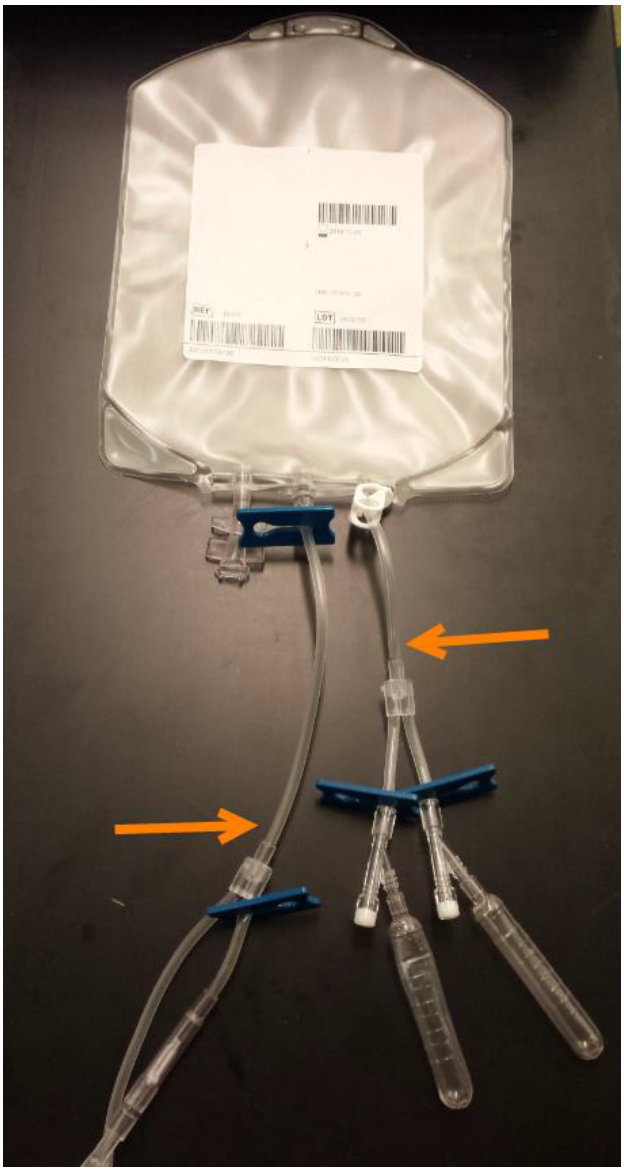

Figure 1. Spectra Optia Collection Set. Seal lines as indicated by arrows.

7.10. Disconnect the subject from the tubing set and provide care per institutional policy.

7.11. Complete all remaining fields of the MNC Collection Procedure Record and make a copy of the document to ship with the product. Refer to **Attachment A** for an example of the **MNC Collection Procedure Record**.
NOTE: Instructions on how to complete the MNC Collection Procedure Record can be found on the backside of the form.

7.12. Email a copy of the MNC Collection Procedure Record to the Sponsor.

7.13. Immediately package the MNC product for shipment using the instructions in Section 8.

7.14 Dispose of the tubing set following institutional policy.

8. PACKAGING AND SHIPPING THE MNC PRODUCT

8.1. Package the MNC product as soon as possible after the collection is completed.

8.2. Retrieve the MNC shipping container and shipping supplies from designated storage area. Verify that there is one MNC shipping container, one 12x12inch absorbent sheet, one specimen transport bag and one temperature data logger available.

8.3. Inspect the MNC shipping container and supplies for damages
If the MNC shipping container and/or supplies are free of damages, proceed to Step 8.4. If the MNC shipping container and/or supplies are damaged, discard and begin at step 8.1.

8.4. Label the MNC shipping container with the verified Dana-Farber Manufacturing facility shipping address label

8.5. Insert the MNC product into the specimen transport bag with the MNC Bag Label facing outward.
NOTE: MNC Bag Label should be visible and not obstructed. The label should be facing the side of the specimen transport bag without the biohazard print so the label is legible while inside the bag.

8.6. Insert the absorbent sheet into the specimen transport bag, making sure not to obstruct the MNC Bag Label

8.7. Verify that both the MNC product and absorbent sheets are placed inside the specimen transport bag and not in the outer document sleeve of the specimen transport bag.

8.8. Expel the air from the specimen transport bag and seal the bag

8.9. Activate the temperature data logger

8.11. Open the corrugated sleeve of the MNC shipping container.

8.12. Carefully, remove the shipping container lid with the silver foil and place foil side down on a hard, flat, clean surface. The white actuator button should be pointing up.

8.17. Place a copy of the MNC Collection Procedure Record on top of the cooling Engine. The Courier Waybill and documentation is included in the package but outside of the actual container. As above, please email CMCF-FORM-0546 to CMCF NCT lab ahead of actual courier pickup.

8.18. Close the package and insert the flaps. Tape the lid shut in the appropriate locations.

8.19. Label the top of the package with the completed courier shipping documentation.

8.20. The package is now ready for courier pickup.

ATTACHMENT A: CLINICAL MNC COLLECTION RECORD

MNC COLLECTION PROCEDURE RECORD

Name: _____
Date of Birth: _____
Study ID Number: _____

- **COLLECTION CENTER NAME**
- _____

- **DATE OF COLLECTION**

D	***D***	***M***	***M***	***M***	***Y***	***Y***	***Y***	***Y***

Gender: Male Female

Subject Weight: _____kg
NOTE: Round to the nearest kilogram (kg).
How was subject identity verification performed:

☐ Photo ID ☐ Hospital ID ☐ Verbal Verification

Verification
Verified By: _____ Date:_____ Time:_____

MNC COLLECTION INFORMATION

MNC Collection Equipment: ☐ Spectra Optia ☐ Other

Device programmed to collect MNC: ☐ YES ☐ NO

Venous Access: ☐ Peripheral ☐ Central Venous Catheter

Line Placement Date (if known):_____

WBC:	PLT:	HGB:	HCT:	TBV:
_____K/mcL	_____K/mcL	_____g/dl	_____%	_____mL

Collection Start Time: _____

Collection End Time: _____

Whole Blood Volume Processed: _____mL

Total AC in Product: _____mL

Collect Volume:	+	Autologous Concurrent Plasma Volume:	=	Total Product Volume:
_____mL		_____mL		_____mL

MNC COLLECTION SUMMARY

MNC Bag Label affixed to collection bag and all patient identifiers are legible and have been verified.	PASS	FAIL
Anticoagulant used: Anticoagulant Citrate Dextrose, Formula A (ACD-A) only.	PASS	FAIL
Target volume of autologous concurrent plasma (150 mL) collected and in collect bag.	PASS	FAIL
Total product volume does NOT exceed 450mLs.	PASS	FAIL
Proximal seals to the collection bag are hermetic. Only heat seals and metal clips are acceptable.	PASS	FAIL

COMMENTS

☐ N/A

_____

_____

_____

_____

OPERATOR INFORMATION

Completed By: _____

Date: _____

ATTACHMENT B: CLINICAL MNC COLLECTION BAG LABEL

MONONUCLEAR CELLS (MNC) BY APHERESIS
FOR FURTHER MANUFACTURING USE OF
TriPRIL CAR T CELLS DRUG PRODUCT
FOR AUTOLOGOUS USE ONLY
NOT EVALUATED FOR INFECTIOUS SUBSTANCES

SUBJECT STUDY NUMBER: _____

NAME:_____

DATE OF BIRTH: _____

SUBJECT DIN: _____

DATE OF COLLECTION: _____
DD/MMM/YYYY

MNC, A Volume (mL): _____

Store at 1 - 10º C until Processing

Must be processed within 48 hours of MNC collection

ATTACHMENT C: SCHEDULE CONFIRMATION FORM

SCHEDULE CONFIRMATION FORM

SUBJECT STUDY NUMBER_____

SUBJECT DATE OF BIRTH:

D	***D***	***M***	***M***	***M***	***Y***	***Y***	***Y***	***Y***

CLINICAL SITE INFORMATION

SITE NAME _____
SCHEDULING CONTACT PERSON_____

SITE DELIVERY ADDRESS:

DELIVERY CONTACT INFORMATION:

LEUKAPHERESIS COLLECTION SCHEDULE

COLLECTION DATE AND TIME:

COURIER SCHEDULE

COLLECTION PICKUP DATE AND TIME:

MANUFACTURING

MANUFACTURING FACILITY DELIVERY ADDRESS:

CLINICAL TEAM SCHEDULING

FORM COMPLETED BY _____

DATE _____

Note: The CRA will fill out this form and send it to CTTL staff. For the most recent version, please reach out to the sponsor.

ATTACHMENT D: CMCF-FORM-0546 TriPRIL CAR T Process Order (v.00 shown below as example)

PRINT RESET

Dana-Farber Cancer Institute | Connell and O'Reilly Families Cell Manipulation Core Facility

450 BROOKLINE AVE, BOSTON, MA 02215

TRIPRIL CAR T PROCESS ORDER

DOC #: CMCF-FORM-0546	REVISION #: 00	PROTOCOL #: 20-518

Recipient/Product Information			
Recipient Name:		Unit # (DIN):	
MGH MRN:		Date of Birth:	
Date of Anticipated Infusion:		Recipient Weight:	kg.
		Date Weight was Obtained:	
Dose Level:	☐ Dose Level -1: 3.0 x 10^7 Total CAR+ T Cells (± 20%) ☐ Dose Level 1: 1.0 x 10^8 Total CAR+ T Cells (± 20%) ☐ Dose Level 2: 3.0 x 10^8 Total CAR+ T Cells (± 20%)	Study ID:	

PROCESS ORDER

Product:	MNC, Apheresis (Autologous)
Date of Collection:	
Directions: Process according to protocol and SOP.	

Scan and Email this Completed Form to: DFCICMCFLabNCT@partners.org
Or FAX to: (617) 632-5759, ATTN NCT Lab

This document must be submitted prior to product collection.
Products will not be processed until this document is received.

Responsible Party Completing the Order and Physician's Signature

Requisition Completed By / Date / Time
Physician Signature / Date / Time

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Note: The CRA will send the patient information and DIN to CMCF via e-mail as soon as they become available. The CRA will then fill out this form, have PI sign, and send it to CMCF by

Emailing DFCI CMCF Lab NCT email distribution list (DFCICMCFLabNCT@partners.org).
For the most recent version of this form, please reach out to CMCF.