Novartis Leukapheresis Reference Manual G3
Summary of Changes Applicable to IU Health
12/8/2021

Pre-Collection

1. Acute infection is defined as within 7 days of collection.
2. Notification of Novartis is required if the donor has symptoms of infection prior to collection or within 48 hours after collection, positive blood cultures, or contamination of the venous catheter.
3. Added guidance on the use of polatuzumab.

Collection

1. Guidance added if the peripheral CD3 and ALC do not agree to use CD3 result to estimate total blood volumes to collect
2. New collection optimization techniques listed
3. If there is a kit or instrument leak or malfunction, Novartis must be contacted.
4. Contact Novartis if there are any Sterility issues or COI (Chain of Identity) issues
5. Rounding up of cell collection numbers is permissible but when medically possible a second collection is preferred.

Cell Processing

1. Optimal target final WBC concentration and acceptable range updated.
2. Cryopreserve in at least 2 bags
3. Do Not write on the bag or cassette
4. Multiple collections on the same patient must be cryopreserved separately
5. Cryopreserved product and cryovials only need to be in LN2 vapor phase for 1 hour prior to packing for shipment to Novartis rather than the previous 8 hours requirement.
6. Novartis must be contacted in case of instrument malfunction/failures
7. "Dry Shipper Container Label" now called "Do Not X-Ray label"
8. Removed requirement to remove shipper labels from transit to the lab before packing shipper for return. Example of this would be a sticker with incoming flight information.
9. Recommended best practice to freeze the same day as collection when possible.
10. Recommended best practice to reduce WBC to < 200e+06 with an electrolyte solution containing protein
11. Recommended best practice to pre-chill centrifuge to 2-8°C if centrifugation is necessary.

The Novartis Leukapheresis Reference Manual G3 is attached for your review. The full Summary of Changes prepared by Novartis is at the end of the document.

Signature Page

For the Novartis Leukapheresis Reference Manual

CAR-T

(KYMRIAH/Tisagenlecleucel/CTL019 and clinical CAR-T cell products)

Version G3

This signature page is used to record the approval of the Novartis Leukapheresis Reference Manual: CAR-T (KYMRIAH/Tisagenlecleucel/ CTL019 and clinical CAR-T cell products) vG3.

The approvals are appended as Novartis PKI electronic signatures.

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Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Shipment documentation and Labeling	N/A	Added requirement: The time the loaded dry vapor shipper is released to the courier must be documented on institutional forms. This information will need to be entered into CellChain™.	Clarification of documentation requirements.
Appendix 1: Leukapheresis in Small Patients			
All sections	Previously Appendix 3.	Moved to Appendix 1.	To fit the new structure of the manual.
Recommendations	Included guidance on: specific catheter choice for venous access, raising hematocrit in "low-weight children", and IV calcium/ magnesium supplementation.	Removed listed guidance.	To generalize recommendations.
Appendix 2: Packing and Shipping: evo® DV10 Dry Vapor Shipper			
All chapter sections	Requirements and guidance on packing and shipping using the evo® DV10 were contained in a separate Addendum to the manual.	All updated information on the evo® DV10 is included in Appendix 2.	Integration of information in the Addendum for the new shipper to be implemented.
Appendix 3: Use of Novartis Hangtags			
All chapter sections	Previously Appendix 5.	Moved to Appendix 3.	To fit the new structure of the manual.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Preparing for Shipment of Leukapheresis Material	Requirement: A maximum of 10 cryobags per patient may be sent to Novartis.	Updated wording to: A maximum of 10 cryobags may be sent to Novartis for manufacture	Clarification of requirement.
Overview of the Cryoport Dry Vapor Shipper	Overview of the current Cryoport shipper was provided in the "Receipt of the Dry Vapor Shipper" section.	Created a new "Overview" section, which also includes the updated Cryoport dry vapor shipper improvements and photos – hinged lid, temperature monitor placed in lid, easier way to secure tamper-evident serialized zip tie.	Better flow of manual and to provide instruction on the new Cryoport dry vapor shipper.
Receipt of the Cryoport Dry Vapor Shipper	N/A	Added a note that shipping information may be on both the waybill and Shipper Certification Form.	Clarification of location of shipping information.
Receipt of the Cryoport Dry Vapor Shipper; Shipment Documentation and Labeling	Requirement: Remove or deface transit stickers from the outside of the empty shipper (it is possible that there may be attached flight number stickers).	Removed requirement.	Prior labels no longer need to be removed or defaced.
Packing the Leukapheresis Material and Sentinel (QC) Vials in the Cryoport Dry Vapor Shipper	Requirement to confirm correct labeling and COI on the cryobags prior to packing.	Updated requirement to include that labeling and COI on the sentinel (QC) vials must also be verified.	Clarification of COI requirements.
Packing the Leukapheresis Material and Sentinel (QC) Vials in the Cryoport Dry Vapor Shipper	N/A	Added requirement: At all times, minimize the amount of time the dewar lid is open.	Update of requirements.
Packing the Leukapheresis Material and Sentinel (QC) Vials in the Cryoport Dry Vapor Shipper; Closing and Sealing the Cryoport Dry Vapor Shipper	Pictures and notes on the packing, closing, and sealing steps were presented as guidance.	Pictures and notes on the packing, closing, and sealing steps are presented as examples of requirements.	To clarify requirements vs. guidance.
Closing and Sealing the Cryoport Dry Vapor Shipper	Included instruction on closing the current dewar.	Added instructions, including new pictures, for closing and sealing the updated dewar.	Incorporation of instruction on a new dewar to be implemented.
Closing and Sealing the Cryoport Dry Vapor Shipper	Included examples of closing the metal and rubber latches.	Removed example of metal latches.	Metal latches are no longer used on the shipping container.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Storage of Cryopreserved Cells	Requirement: Store cryopreserved leukapheresis material and sentinel (QC) vials in a temperature-monitored system at a temperature less than or equal to minus 120°C (eg, liquid nitrogen).	Updated requirement for sentinel (QC) vials to: Store cryopreserved sentinel (QC) vials at ≤ −120°C, or using a cryogenic storage method approved by Novartis, until packing for shipment.	Updated requirement to allow sentinel (QC) vials to be stored separately.
Storage of Cryopreserved Cells	Requirement: After CRF is completed, equilibrate leukapheresis material for a minimum of 8 hours prior to shipping.	Updated requirement to: After CRF is completed, equilibrate leukapheresis material for a minimum of one (1) hour prior to shipping.	Updated research by Novartis.
Documentation of the Cell Processing Procedure	The volume of leukapheresis material collected was an example of required documentation.	Additional example was added indicating that the volume within each cryobag must be documented.	Clarification of requirements.
Routine Data and Nonroutine Event Reporting	Listed several examples of reportable issues.	Added that sites must contact Novartis in case of instrument malfunctions/ failures.	Clarification of reporting requirements.
Best Practices for Cell Processing/Cryopreservation of Leukapheresis Material	N/A	Added recommendation: It is recommended to cryopreserve the sentinel (QC) vials along with the cryobags in the same cryopreservation procedure/run.	Clarification of guidance on cryopreservation.
Packing and Shipping: Cryoport Dry Vapor Shipper			
All chapter sections	Guidance and examples were located in Appendix 6: Guidance on Packing for Transport.	Incorporated guidance and examples into main chapter sections.	Better flow of manual – per recommendations from treatment centers.
All chapter sections	Noted that instructions for shipment using the new evo® DV10 dry vapor shipper would be forthcoming.	Removed notes.	Instructions for the evo® DV10 are now included in the manual (Appendix 2).
All chapter sections	Referred to the "Dry Shipper Container Label".	Updated label name to "Do Not X-Ray label".	Consistency in label name terminology.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Cryobag and Sentinel (QC) Vial Labeling	Requirement: Sentinel (QC) vials must be labeled with an affixed/attached label.	Updated requirement to: Sentinel (QC) vials must be labeled legibly prior to cryopreservation.	Sentinel vials no longer need affixed/attached label.
Cryobag and Sentinel (QC) Vial Labeling	N/A	Added requirement: The DIN/SEC/institutional assigned Apheresis ID entered into CellChain™ during data reporting must match that on the cryobag and sentinel (QC) vial labels.	To ensure accurate labeling and Chain of Identity.
Cryopreservation	Listed requirements for cryopreservation.	Rearranged list of requirements.	To improve flow of manual.
Cryopreservation	N/A	Added requirement: Multiple collections for the same patient must be cryopreserved separately.	To clarify requirements for separate processing and cryopreservation of multiple collections.
Cryopreservation	Guidance: Writing on or labeling of metal cassettes is not recommended.	Changed to a requirement: Avoid writing on metal cassettes.	Change from guidance to a requirement.
Cryopreservation	Requirement: Only one patient's leukapheresis material may be cryopreserved in a controlled-rate freezer chamber at the same time.	Changed to guidance: Only one patient's leukapheresis material should be cryopreserved in a controlled-rate freezer chamber at the same time to prevent mix-ups.	Change from requirement to guidance only.
Cryopreservation	Requirement: Sentinel (QC) vials must be cryopreserved with the leukapheresis material cryobags.	Changed to guidance: It is recommended to cryopreserve the sentinel (QC) vials along with the cryobags in the same cryopreservation procedure/run.	Change from requirement to guidance only.
Cryopreservation	Requirement: Following CRF leukapheresis material and sentinel (QC) vials must be stored to equilibrate to cryopreservation temperatures.	Updated requirement to: Following CRF the cryopreserved leukapheresis material and sentinel (QC) vials must be stored to equilibrate to cryopreservation temperatures for at least one (1) hour.	Updated research by Novartis.
Cryopreservation	Included an example CRF program.	Updated steps in the example program.	Clarification.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Leukapheresis Cell Processing			
All chapter sections	Guidance and best practices were located in Appendix 4: Cell Processing Guidance.	Incorporated guidance and best practices into main chapter sections.	Better flow of manual – per recommendations from treatment centers.
Cell Processing	For the cryoformulation, provided a "target final WBC concentration" and "optimal target range".	Updated to "optimal target final WBC concentration" and "acceptable range".	To clarify the preferred WBC concentration for the cryoformulation.
Cell Processing	N/A	Added recommendation to cryopreserve in at least 2 cryobags when possible.	Update of guidance.
Cell Processing	Requirement: Open manipulation of the leukapheresis material must be performed using aseptic techniques in a class II biological safety cabinet International Organization for Standardization (ISO) class 5 environment.	Updated requirement to: Open manipulation of the leukapheresis material must be performed using aseptic techniques in an International Organization for Standardization (ISO) Class 5 environment (for example, a class II biological safety cabinet).	Clarification of requirement- a class II biological safety cabinet is an example of an ISO Class 5 environment.
Cell Processing	Requirement: Novartis must be notified if the cell concentration falls outside of the target range.	Removed requirement.	The WBC concentration will be calculated and reported in the updated version of CellChain™.
Cell Processing	Requirement: A maximum of 10 cryobags per patient may be sent to Novartis.	Updated wording to: A maximum of 10 cryobags may be sent to Novartis for manufacture.	Clarification of requirement.
Cell Processing	Provided an example picture of a cryobag.	Updated picture of cryobag; list of example cryobags remains unchanged.	To improve image quality.
Cell Processing	Sentinel (QC) vials must be collected.	Added requirement that leukapheresis material collected in the sentinel (QC) vial must have the same cryoformulation and WBC concentration as that in the cryobags.	Clarification of sentinel (QC) vial collection requirements.
Cryobag and Sentinel (QC) Vial Labeling	Requirement: Avoid writing directly on the surface of the bag.	Updated requirement to: Do not write directly on the surface of the cryobag.	Emphasis and clarification of requirement.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Leukapheresis Collection	N/A	Added a note to contact Novartis Cell Therapy Operations to discuss collection optimization and strategies to prevent overcollection.	To provide additional guidance.
Routine Data and Nonroutine Event Reporting	Listed several examples of reportable issues.	Added that sites must contact Novartis for a leak in the apheresis kit, and instrument malfunctions/ failures.	Clarification of reporting requirements.
Leukapheresis Material Transfer and Testing			
All chapter sections	Requirements and guidance were spread between the Specifications, Collection, and Cell Processing chapters, and Appendix 1.	Created a new dedicated chapter on leukapheresis material transfer and testing. Included a copy of the updated specification table from the Leukapheresis Material Specifications chapter and instructions on when to contact Novartis.	Better flow of manual – per recommendations from treatment centers.
Leukapheresis Material Testing	N/A	Added requirement: Prior to removing a sample of leukapheresis material for testing, the cell suspension must be gently mixed to ensure that a representative sample is tested.	Update of requirements on leukapheresis material testing.
Leukapheresis Material Testing	N/A	Added note: For clinical trials, please also refer to your Novartis Clinical Trial Protocol for additional testing that may be required.	To account for potential additional testing requirements in clinical trials.
Routine Data and Nonroutine Event Reporting	Section was included in Collection and Cell Processing chapters.	Included section in current chapter, with examples to contact Novartis in case of contamination, sterility failures, COI breaches, and instrument malfunctions/ failures.	Clarification of reporting requirements.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Leukapheresis Collection			
Guidance on Peripheral Blood Testing; Leukapheresis Collection	Guidance was located in Appendix 2: Peripheral Blood Testing and Cell Collection Optimization Guidance.	Incorporated guidance into main chapter sections.	To improve flow of the manual.
Guidance on Peripheral Blood Testing	Table 1 provided guidance on TBV to process for "adult sized" patients.	Table 1 guidance is applicable for all patients (ie, removed "adult-sized"). Added note: If the ALC is not equivalent to the CD3+ count, use the CD3+ count to estimate TBV.	Clarification of guidance on peripheral blood count testing as table applies to both the adult and pediatric collections.
Identity Verification and Collection Bag Labeling	Requirement: Avoid writing directly on the surface of the bag.	Updated requirement to: Do not write directly on the surface of the bag.	Emphasis and clarification of requirement.
Identity Verification and Collection Bag Labeling	N/A	Added requirement: Multiple collections on the same day must be documented and each must be labeled with a unique DIN/ SEC/ institutional assigned Apheresis ID.	Clarification of requirements for labeling of multiple collections.
Leukapheresis Collection	Requirement that apheresis systems must be approved by local health authorities.	Added examples of apheresis systems (Spectra Optia®, Fenwal Amicus®, ComTec®).	To provide examples of apheresis systems.
Leukapheresis Collection	N/A	Added notes that the Spectra Optia® CMNC or MNC program may be used.	Clarification of allowable processes.
Leukapheresis Collection	Guidance: If using the Terumo BCT Collection Preference Tool, the 4th color from the left is preferred.	Added an image of the Collection Preference Tool with the preferred collection preference marked. Added a reference to Terumo BCT Document #361 for further guidance.	Clarification of guidance.
Leukapheresis Collection	N/A	Added a list of additional optimization techniques to consider.	To provide further guidance on optimization of collection.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Guidance for Patient Infectious Disease Testing	N/A	Added note: Interpretation of infectious disease test results is the responsibility of the medical institution and medical professionals treating the patient.	Clarification of who is responsible for determining patient eligibility for collection.
Guidance for Patient Infectious Disease Testing	Included guidance on interpreting HBV testing results.	Added an additional reference from the CDC on interpreting HBV test results.	To provide additional guidance on determining patient eligibility for collection.
Guidance for Patient Infectious Disease Testing	Guidance on HCV and HIV testing was in separate memorandum, dated 08-July- 2021.	Added HCV and HIV guidance from the memorandum, as well as an additional reference from the CDC on interpreting HCV test results.	Integration of the memorandum for clarification and further guidance on determining patient eligibility for collection.
Precollection: Determining Patient Readiness for Leukapheresis			
Informed Consent for Clinical Trials	Indicated that a patient's leukapheresis material would be reviewed for acceptance.	Removed wording.	To align with updated Novartis processes.
Initial Health Assessment	Patients with an acute infection (bacterial, viral or fungal) or a positive blood culture should not undergo leukapheresis collection.	Added examples of positive culture results; clarified that an acute infection is within 7 days of leukapheresis collection.	Clarification of requirements on patient infection prior to collection.
Initial Health Assessment	N/A	Added requirement: If there are any signs/ symptoms of infection, pre-collection or within 48 hours post-collection (eg, temperature, positive blood culture) in the patient, or contamination of the venous access catheter, please notify Novartis Cell Therapy Operations.	Clarification of requirements on patient infection prior to collection.
Initial Health Assessment	N/A	Added guidance on asymptomatic viral infections (eg, COVID-19, Zika).	To provide additional guidance on patient infection prior to collection.
Current and Previous Therapy Timing	N/A	Added guidance on polatuzumab.	To highlight key washout timing recommendations.

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Leukapheresis Material Specifications			
Summary of Leukapheresis Material Specification Requirements	Table 1: Leukapheresis material specification requirements.	Updated Table 1 to include that patient infectious disease testing must be completed within 30 days of collection; added a footnote for additional information.	Clarification of requirements.
Summary of Leukapheresis Material Specification Requirements	Cryobag acceptance criteria: intact bag/ports.	Updated acceptance criteria to indicate that cryobags must have hermetically sealed ports.	Clarification of specification requirements.
Collection Cell Counts	Guidance was located in Appendix 1: Guidance on Leukapheresis Material Specifications and Testing.	Incorporated guidance into main chapter section.	To improve flow of manual.
Collection Cell Counts	N/A	Added guidance on reviewing and reporting the WBC differential of collected leukapheresis material.	To provide additional guidance on collected cell counts.
Collection Cell Counts	Defined Excess Leukapheresis Material.	Added guidance: Excess Leukapheresis Material may be requested to be split into 2 batches.	Clarification of guidance.
Collection Cell Counts	Guidance: Rounding rules may be applied.	Added a note that when medically possible, it is preferred to perform an additional collection to achieve the minimum specification values.	Clarification of guidance.
Collection Cell Counts	Note to contact Novartis if less than 1.5 x 10^9 or greater than 4 x 10^9 CD3+ cells.	Updated the lower bound of the collected cell range to 1.0 x10^9 CD3+ cells.	Update of requirement.
Patient Infectious Disease Testing			
All chapter sections	Requirements and guidance on patient infectious disease testing were in the Specifications chapter and Appendix 1.	Created a new dedicated chapter on patient infectious disease testing.	Better flow of manual – per recommendations from treatment centers.

Change History for Global Leukapheresis Reference Manual Version G3

Chapter/Section	Previous Version: Global G2	Current Version: Global G3	Justification
Global and Introductory Changes			
All	All sections.	Content throughout was edited and streamlined.	To ensure accuracy, increase clarity, and improve content flow.
All	Included a Table of Contents for each chapter and appendix.	Includes only a main Table of Contents.	Simplification based on treatment center feedback.
All	Requirements were in main chapters; guidance and examples were in appendices.	Guidance is incorporated sequentially into each main chapter. Previous Appendices 1, 2, 4, and 6 were removed as all content was moved.	To improve flow of the manual based on how the patient and collected leukapheresis material moves through the CAR-T cell process.
All	Specific icon was used to highlight differences and notes for clinical trials.	Removed icon; information for clinical trials is called out in green font.	To add clarity.
All	Used terminology "Novartis Online Portal".	Updated terminology to "CellChain™".	Clarification of data entry location.
All; Chain of Identity	Used terminology "Institutional assigned ID".	Updated terminology to "Institutional assigned Apheresis ID".	Clarification of patient identifiers.
Introduction	Included global contact phone numbers.	Updated contact information to include additional global contacts and email addresses.	Update.
Definitions	Defined the "Start of the cryopreservation procedure".	Updated the definition as the "Cryopreservation Date/Time". Added new definition for "Collection Date/Time".	Clarification of key definitions.
Chain of Identity	Definition indicated the DIN was assigned by the ISBT-128 labeling process.	Clarifies that the DIN is assigned by the site using ISBT-128 labeling processes.	Clarification of COI definition.
Chain of Identity	Defined Novartis Batch Number.	Clarifies that the Batch may include more than 1 leukapheresis collection from the same patient.	Clarification of COI definition.

Guidance for attaching the Novartis Hangtag Label

Perform steps 1 and 2 prior to removing the cryobags from the freezer:

1. Verify accurate printing of the hangtag label, including unique patient identifiers and cryobag identification information reported in CellChain™
    - If an error is identified, immediately contact Novartis Cell Therapy Operations. Do not attach an incorrect hangtag label to a cryobag

2. Precool the labeled hangtags by placing in dry ice or a freezer. Hangtag labels should be precooled for at least 10 minutes

Perform steps 3 and 4 during the first step in the cryobag/cassette packaging process:

3. Attach each precooled hangtag label to the corresponding cryobag. Novartis provides hangtag fasteners for this purpose
    - Ensure that the cryobag number on the hangtag label corresponds to the cryobag number on the institutional label
    - Hangtag labels must be attached to the cryobag
        - If institutional protocol requires cryobags to be cryopreserved inside an outer overlay bag, the hangtag label may be attached to the outer bag. If the overlay bag cannot accommodate the hangtag label, remove the overlay bag (as this is not required by Novartis), attach the hangtag label, and continue the packaging steps

4. Verify and document that the unique patient identifiers and cryobag information on the attached hangtag label match those on the institutional label