Methodist Health Services Corporation & UnityPoint Health Methodist	Page # 1 of 5	Section: Cell Processing	Policy #: CP:013.19
	Approved by: see signature block at end of policy		Date created: 3/11/99
Laboratory CELL PROCESSING	Date Revised: 7/23/99, 9/9/99, 1/15/04, 3/8/04, 5/20/04, 7/18/04, 10/15/04, 2/14/08, 4/15/08, 1/21/09, 3/5/09, 3/19/09, 4/02/09, 6/17/09, 5/17/10, 5/20/12, 3/14, 7/11/16, 4/19/17 Date Reviewed:		
	Policy/Revision Submitted by: Deb Rinne CLS		
	JCAHO Standard: NA		

POLICY GUIDELINE ON: **Quality Management Program**

I. POLICY:

The Hematopoietic Cell Processing Laboratory Quality Management Program is designed to assure products are of the utmost Integrity for engraftment by ensuring reliable and effective processes.

II. PURPOSE:

To be certain that processes are in place which ensure maximum potency, sterility, and safety in the processing and storage of hematopoietic progenitor cells.

III. GENERAL INFORMATION:

A. See page one of Cell Processing Laboratory Standard Operating Procedures manual for Cell Processing Laboratory Organizational structure.
B. No formal agreements are necessary between the Collection area, Processing area, and Clinical Transplant area, as all are part of the same facility – Methodist Medical Center.
C. This program monitors pre-analytical, analytical, and post-analytical processes to assure quality. Outcome analysis is part of the post-analytical process.
D. These processes consist of equipment checks and preventative maintenance, reagent integrity, policy and procedure review, tests for functional integrity of products, error detection and correction, adverse reaction review, and review of engraftment times.
E. The Cell Processing Laboratory Medical Director is a licensed physician directly responsible for all medical aspects related to the Cell Processing Laboratory.
F. The Cell Processing Laboratory Director is responsible for all procedures and policies, including the Quality Management plan, plus administrative operations of the Cell Processing Laboratory,. Result review for all processes is accomplished through the Cell Processing Laboratory Director.
G. The Laboratory Quality Management Coordinator designee establishes and maintains systems to review, modifies as necessary, and approves all policies and procedures intended to monitor compliance with regulatory requirements, and the performance of quality audits.
H. The Laboratory Quality Management designee is responsible for review of the monthly Quality Management Review report (CP: 055). After review of all problem logs, the designee reviews the resolutions. If any ongoing problems occur, cell processing personnel will consult with manufacturers, other cell processing laboratories, Methodist Biomedical Department or other individuals to find resolutions.
I. All tests and procedures for processing, testing, and storage of the products essential to the evaluation of their safety and usefulness are part of the laboratory and/or patient permanent record.
J. Document Control is outlined in Section IV.D.

IV. PROCEDURE:

A. Pre-analytical assessment / Process Control

1. Environmental monitoring in the Cell Processing Laboratory
   - Temperature should be 65-75ºF (18-24ºC). Record daily on CP:073 Hood/Benchtop Cleaning/Temperature / Humidity
   - Record when processing product.Humidity should be 25-65%. Record daily on Hood/Benchtop Cleaning/Temperature / Humidity Record when processing product.
   - Ventilation is handled by MMCI Facility Services. The Air Handler Equipment Report is available from Facility Services.

- Air quality - Listed under Equipment annual checks below for laminar flow hood cultures and air cultures.
- Surface contaminants – Listed under Equipment day of use checks below for laminar flow hood and bench top cleaning and SOP CP:004 Sterile Technique in the Cell Processing Laboratory.

All entering of reagents and product (open steps) is accomplished under the laminar flow hood.

2. Equipment

Equipment quality control and preventative maintenance are performed to assure properly functioning equipment documented on CP: 081 and CP: 062.).

Refrigerators and freezers used for the storage of specimens, hematopoietic progenitor cell products, or reagents shall not be used for any other purpose. The equipment checks and preventative maintenance are performed and documented on the patient daily checklist (CP:031) and on equipment logs (CP: 065, CP:069) as appropriate.

- Refrigerator for proper temperature of freezing media.
- Freezer temperature for assurance of frozen cold block for use when adding freezing media to product
- Liquid nitrogen storage unit levels and continuous recording of LN2 vapor temperatures for product storage safety
- Liquid nitrogen storage tank gauges check to assure ready supply of LN2

a. Day of use checks include:

- Cleaning of laminar flow hood and processing bench top
- Tube sealer for accuracy in making complete seal
- Cryomed recorder for proper range of temperatures required for freezing process
- Laminar airflow hood magnehelic gauge for visual check of pressure between blower and Hepa filter
- Programmable freezer for intact probe for freezing reliability
- Ohaus balance for assurance of proper product weights
- LN2 tank check for proper LN2 delivery to freezing chamber before first day of use

b. Annual checks include:

- Laminar air flow hood inspection by Clean Air Flow, Inc. to ensure an ultra-clean work station for sterile media preparation
- Laminar air flow hood cultures
- Processing lab air culture
- Cleaning and power cord inspection
- Thermometers used in refrigerator and freezer by an NIST thermometer
  Ohaus balance by Biomedical t using annually calibrated weights.
- Electrical equipment maintenance is through maintenance and biomedical engineering departments who perform annual checks on all electrical instruments, plus respond to any equipment problems.
- Quality control on freezing chamber vs. controller display, storage units temperatures and alarms, and transport container is performed annually.

c. The Equipment Problem Log (CP: 064) is to be completed when there is an equipment problem.

3. Reagents and supplies

- Reagents are checked for bacterial growth , turbidity, abnormal color, breakage of seals, and damage as they come into inventory and are documented as acceptable or unacceptable on Receiving Record of Reagents and Supplies (CP:060).
  Any reagent or supply deemed unacceptable will be documented on the Reagent / Supply Problem Log (CP:061) as to the reason and the follow-up.
- Sterility of supplies is ensured by not using any supply in which sterility is under question.
- Reagents are stored at correct temperatures to reduce contamination.
- Expiration dates are observed.

a. All supplies and reagents used in cell processing are stored in a safe, sanitary, and orderly manner, ensuring sterility and are used in a manner consistent with manufacturing instructions.

b. Reagents used are documented in medical literature as safe and effective in preserving hematopoietic progenitor cells. Engraftment has been proven using these reagents.

c. Critical reagents and supplies (DMSO, 0.9% NaCl, heparin sodium, cryocyte freezing containers) lot numbers and expiration dates are documented on the patient's daily Processing Report. Pheresis kit lot number and expiration date from collection area are stored in patient file.

d. Labels are tested in vapor and liquid LN2 for reliability before use when there is a change in manufacturers or materials. Approval of labels and any changes associated with them are filed with dates in use and dates removed from use (obsolete). Any extra obsolete labels are destroyed.
e. Inventory control is accomplished through weekly review and ordering of all needed reagents and supplies. . A record is kept of the requisition number for product tracking purposes. The requisition number allows the product to be traced from ordered to received, or backordered, if applies.

4. Policies and procedures
   a. Policies and procedures are reviewed by the Cell Processing Laboratory Director biannually and when changes are made.
   b. Personnel performing procedures read and sign any changes made in policies and procedures before changes go into effect. Any deviation from Standard Operating Procedures is documented and action taken, if necessary.
   c. Forms are reviewed anytime a revision occurs.

5. Any new process to be developed is accomplished by Cell Processing personnel as assigned by the Laboratory Director or Laboratory Medical Director. Documentation will take place on a New Process Development Schedule (CP: 076).

6. Any planned deviation (CP: 077)from Standard Operating Procedure shall be pre-approved by the Processing Facility Director or designee and if medically relevant, by the Processing Facility Medical Director or designee. Document on CP: 077 Planned Deviation Form.

7. Personnel qualifications are listed in Methodist Health Services Corp. Position Description / Performance Review & Development Plan. For Training / Competency / Proficiency assessment and continuing education of cell processing personnel, see CP: 024.

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8. Validation and qualification of critical supplies, reagents, equipment, procedures, and facilities are performed. This includes a change in manufacturers for cryocyte freezing containers, DMSO, and new freezing equipment. Critical procedures include processing techniques, cryopreservation protocols, storage conditions, and transportation. Split samples are to be used as a method of evaluation where applicable. Validation Protocol policy CP: 022 applies. Evaluation of protocols is reviewed with documentation of approval by the Quality Management Coordinator designee.

B. Analytical Assessment / Process Control

1. Suspected adverse reactions or occurrences during collection
   A suspected adverse reaction, occurrence, or equipment problem during collection (as listed on the Adverse Occurrence Form Stem Cell Harvesting kept in the collection area) requires that form be filled out by the collection area and a copy sent to the cell processing laboratory if the problem will in any way concern the lab. It will be determined by the cell processing laboratory director whether or not the product is appropriate for infusion. If the product is not acceptable for infusion, it will be documented on the HPC freezer summary sheet , CP:033 at the front of the patient's file and the patient's physician notified. The form is kept in the patient laboratory record after review.

2. In the instance of a laboratory error, accident, or equipment problem that could affect the product in any way or result in an adverse reaction, documentation will be on the appropriate form (see post analytical assessment forms) and evaluated promptly. Any error which falls within the Biological Deviation reporting criterion will be filed with the FDA. The technical coordinator and Cell Processing Laboratory Director will determine if an error meets the FDA reportable criteria upon review of the error. Corrective actions are documented on the form and reviewed by the Cell Processing Laboratory Director. Depending on the degree of the problem, a Corrective Action Record CP: 075 may be completed per the laboratory director. If the product is not acceptable for infusion, it will be documented on the HPC freezer summary sheet at the front of the patient's file and the patient's physician notified. A process improvement plan will be initiated if deemed necessary.

   a. Patient identification and labeling
      1. See Hematopoietic Progenitor Cell Identification and Labeling CP: 003.
      2. In the event of more than one patient being collected on the same day, to avoid product mix-ups, separate patient labeled trays are used and only one patient's product is on the processing bench at a time. Each patient's product will be processed and transferred to the appropriate labeled freezing container before the next patient is

started.
3. Each significant step is initialed by person performing.

b. Container quality
   1. Sterile bag

c. Product quality / engraftment potential
   1. Total nucleated cell (N.C.) count after collection and after any dilution (if applicable). Comparison is made to previous collection's N.C. count. Greater than 50% difference is recorded in the Discrepant Results Log. Investigation includes a consult with collection area for possible explanation of discrepancy.
   2. Hematocrit assessment
   3. CD34+ enumeration
   4. Cell viability

d. Freezing process monitor
   1. Freezing curve traced by Cryomed programmable controller

e. Measure of sterility
   1. Bacterial and fungal cultures on post processing specimen
   2. See CP: 007 Hematopoietic Progenitor Cell Microbial Cultures for management of positive culture results.

f. Per the Cell Processing Laboratory Director, cell viability and recovery are assured analytically by Flow Cytometry CD34+ counts and Flow Cytometry cell viability testing and post-analytically by engraftment data. Numerous validation studies specifically showing timely engraftment, such as in reagent validation, nucleated cell concentration, freezing container volumes, freezing bag labels, freezing media concentrations, and cryopreservation have been documented.

C. Post–analytical assessment (includes Outcome Analysis)

1. The purpose of our post-analytical assessments is to identify weaknesses in our processes, especially if there are multiple reports of the same nature so changes or corrections can be made. Documentation, corrective action (if applicable), lab director review, and appropriate agency notification (if applicable) will take place.

CP: 032 Hematopoietic Progenitor Cell, Apheresis Processing Report (includes correct product label information)

A second cell processing tech reviews the processing report for calculation accuracy and completeness. Product labeling and the rest of the daily processing paperwork is also double checked. Documentation of this review is on the daily checklist. The Cell Processing Director reviews, signs, and dates the daily paperwork prior to infusion of the product. Any error detected will be corrected before it is reported, or if already reported, at the time of detection. Any error in result reporting is documented on the Deviation from SOP log. The log should be filled out by the person involved in the error. If this is not possible, the person reviewing the paperwork will complete the log.

CP: 049 Adverse Occurrence Form Stem Cell Harvesting (collection area form)

This form is generated by the collection area according to their policy and is forwarded to the Cell Processing laboratory if the occurrence could involve the laboratory in any way. Follow up occurs by lab personnel as necessary.

CP:050 Adverse Occurrence Form Stem Cell Infusion form (transplant area form)

A suspected adverse reaction or occurrence during infusion, if thought to be lab related (as listed on the Adverse Occurrence Form Stem Cell Infusion form kept in the clinical area) requires the appropriate form filled out by the clinical area and a copy sent with the product bags that were infused to the cell processing laboratory.
a. Cell processing lab personnel check the bag(s) for any clerical errors and document any discrepancies on the Adverse Occurrence Form.
b. The Cell Processing Lab Director is notified. If the adverse occurrence is laboratory related, the Cell

Processing Director will detail instructions for a follow-up investigation to cell processing personnel.

c. Evaluation of any reaction is promptly made by the Cell Processing Lab Director on the Adverse Occurrence Form.
d. A copy of the completed Adverse Occurrence Form is sent to the patient's chart for the physician whether or not laboratory follow-up was necessary. The original form is kept in the patient laboratory file.
e. Where applicable, the event shall also be reported to the clinical area, the collection area, and appropriate regulatory agency.

CP: 057 Audit Report Form

10% of charts will be audited annually by Cell Processing Lab Director designee on patients who have undergone transplants. To avoid auditing oneself, the audit will be performed by someone other than personnel performing that day's work. Thus, more than one person may be auditing one patient chart. Documentation of audit review will take place by the Cell Processing Lab Director who is the designee of the Quality Management Coordinator. Twice per year, patient laboratory processing charts will be printed and checked against processing records for accurateness of entry and proper units of each value. Any problems, adverse trends, and improvement opportunities are to be addressed and resolved.

CP: 075 Corrective Action Record for Unplanned Deviation /Adverse Event

The Corrective Action Record for Unplanned Deviation / Adverse Event is to be completed per Cell Processing Laboratory director, depending on the degree of the problem.

CP: 041 Deviations from SOP Log

Any laboratory error or accident along with corrections or adjustments made shall be documented on the Deviations from SOP log. Examples would be a clerical error on the product label, a calculation error on the Processing report, or loss of product volume due to spillage.

CP: 040 Discrepant Results Log

Discrepant Results log is completed when a nucleated cell count is greater than a 50% difference from the previous day's count.

CP: 043 Donor Eligibility / Ineligibility Statement When Communicable Disease Testing Repeatedly Reactive

Any product with a repeatedly reactive communicable disease test will be documented on a Donor Eligibility / Ineligibility Statement When Communicable Disease Testing Repeatedly Reactive form. If product is to be infused, the form is signed by the Cell Processing Lab director and patient's physician and urgent medical need documented. Retain in patient file.

CP: 048 Engraftment Data Review form (Outcome Analysis)

Engraftment times are monitored by the cell processing lab and reviewed by the Cell Processing Lab Director. Engraftment criteria: absolute neutrophil count of >500/uL An absolute neutrophil count (ANC) not reaching 500/ul within 4 weeks of infusion will be recorded on an Engraftment Data Review Form and the Laboratory Director/ Quality Management designee will follow up with the transplant physician. An investigation of laboratory procedure will take place if thought the laboratory error had taken place that would have any bearing on delayed engraftment. Copies of the completed form are kept in the patient's file in the cell processing lab and in patient chart on nursing floor for the physician.

CP: 064 Equipment Problem Log

This log in completed when any malfunction occurs in equipment used in cell processing that could adversely affect the product.

CP: 058 RL Solutions report – enter online.

Any adverse events, including error and accident detection and correction, Biological Product Deviations, or complaints need an RLSolutions report entered online if needs to be documented in the General Laboratory error database. The Blood Bank Clinical Coordinator will make that decision.

CP: 061 Reagents / Supply Problem Log

Any problem detected upon receipt or use of any reagent or supply is documented on this log.

CP: 042 Results of Microbial Cultures on HPC Product and Release Form for Positives

Positive microbial cultures (notified by Microbiology) are documented and on the Record of Positive Microbial Cultures and reviewed. CP:007 is followed.

2. The summary of any reviews listed above is documented on a monthly Quality Mangement Review form: (CP:055)

3. The Cell Processing Director will communicate to cell processing personnel any matter that he feels needs a thorough investigation including resolution and outcome by the Quality Management Department. This includes unexplained discrepant results or failure of a product to meet specifications. Documentation will take place on the Corrective Action Record for Unplanned Deviation / Adverse Event.

4. A written description of any of the above reports is available to the recipient's physician , collection area, or transplant area when appropriate.

D. 1. See Document Control Record for all documents (forms, policies, procedures, and labels) that must adhere to the following requirements:
   a. Policies and procedures must be reviewed every two years and whenever a change is made.
   b. Forms and worksheets must be reviewed every three years or earlier if a change is made.
   c. Revision #, approval date and by whom, effective date, training completion date, and revision description notes and archival dates are recorded on the Document Control Record.
   d. Obsolete documents are removed from the SOP and placed into the Archives file with a "Removed from use" date, along with the initials of the person involved. The obsolete policy, procedure, or form is documented as **Obsolete** on the Document Control Record next to the title of the document. The obsolete documents are archived a minimum of 10 years. The file drawer marked HPC /Cryobank contains the archived and obsolete policies, procedures, and forms.

   e. All policies, procedures, and forms are PDF files. Any changes to be made are possible only by responsible authorized individuals with special access.

   2. Record creation, assembly, storage, archival, and retrieval
      a. Any blank records (created on the share drive) are assembled in the SOP. Additional copies of forms for use during the cell processing procedure are stored in the file cabinet drawer marked "HPC". The black file cabinets contain patient records. For any patient records moved offsite, see CP: 017.

E. Product Tracking

The Patient Summary log in the front of the Freezer Inventory notebook lists patients in order of first day of collection, along with their hematopoietic progenitor cell product number(s). If the product is infused, the infusion date is present. If no infusion date, the product is still in storage. If the product has been discarded / destroyed, this will be indicated and a Record of Discarded / Transferred Products form completed.

V. REFERENCES:

FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration, Fourth Edition, October 2008

MEDICAL DIRECTOR		
DATE	NAME	SIGNATURE
March 4, 2017	Elizabeth A. Bauer-Marsh, M.D.	Elizabeth A. Bauer-Marsh MD
SECTION MEDICAL DIRECTOR		
May 13, 2016	Julia Adams, M.D.	Julia Adams, M.D.

REVISION HISTORY			
Rev	Description of Change	Author	Effective Date
.18	Forms – 3 year review, CP:042 name change, Peminic added & Event Report omitted	D. Rinne	6/1/12
.19	Removed compliance with the foundation for Accreditation of Cellular Therapy Standards and added reference to forms #.	D. Rinne	3/19/14
.20	Added policy/form numbers. Added RL Solutions reports and new medical director.	Deb Rinne	2/23/16
.21	Updated form review and removed BPD from SOP, but added statement to match Blood Bank QM policy on BPD.	Deb Rinne	01/31/17

Reviewed by

Lead	**Date**	**Coordinator/ Manager**	**Date**	Medical Director	**Date**
				D McKinstry MD	6/1/12
		Kathy L. Turpin	3/19/14	D McKinstry MD	3/19/14
D. Rinne	2/23/16	Kathy L. Turpin	6/3/16	Julia Adams, M.D.	7/11/16
D. Rinne	1/22/17	June Bembenek	2/3/17	Julia Adams, M.D.	4/19/17