Pediatric Blood and Marrow Transplant
Adult Blood and Marrow Transplant
Stem Cell Laboratory

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Corrective and Preventive Actions

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COMM-PAS-0152
Corrective and Preventive Actions

1 PURPOSE

1.1 The purpose of this procedure is to provide system instructions and to assign responsibilities for the identification, assignment, implementation, verification, and closure of a Corrective and Preventive Action (CAPA).

2 INTRODUCTION

2.1 This Standard Operating Procedure (SOP) describes the process to be followed for the CAPA process used in the Adult and Pediatric Blood and Marrow Transplant Program (APBMT) and Stem Cell Laboratory (STCL).

2.2 A CAPA process is necessary to mitigate system nonconformities and performance problems with respect to many areas, including but not limited to quality systems, manufacturing, customer complaints, or discrepancies cited during internal and external audits performed at the facility or its associated programs.

3 SCOPE AND RESPONSIBILITIES

3.1 Trained personnel are responsible for completing COMM-PAS-015 FRM1 *CAPA Report* and modifying step routes as needed to ensure the applicable Supervisor/Manager, Subject Matter Expert (SMEs), and Medical Director are included.

3.2 The Medical Director and the APBMT Clinical Quality Program (CQP) evaluate and approve/or reject all CAPAs via electronic signature.

3.3 Operations/Manufacturing responsibilities include:

- Reviewing/approving planned CAPA and recommending changes, as necessary
- Reporting new risks, which may result from a suggested CAPA
- Completing assigned CAPA tasks and reporting the status/completion of CAPA
- Reviewing and recommending changes on the overall CAPA based on review of effectiveness checks
- Participating in determining if any external reporting is required to outside vendors/sponsors of events that may impact products related to their organization

3.4 CQP responsibilities include:

- Tracking open CAPA
- Coordinating with Subject Matter Experts (SME) to review and recommend changes on CAPA, as applicable
- Reviewing, approving, and recommending changes on the overall CAPA based on review of effectiveness checks
- Ensuring implementation of CAPA recommendations

- Determining if any external reporting is required to outside vendors/sponsors of events that may impact products related to their organization
- Reviewing and approving all CAPAs for completeness and appropriate level of detail, including evaluation of risk to affected systems
- Monitoring the CAPA system to facilitate effective management of CAPA and Effectiveness Checks
- Providing status updates to applicable Supervisor/Managers and Medical/Program Directors

3.5 Medical Director (MD) responsibilities include:

- Reporting new risks that can adversely affect a patient's health or medical outcome as a result of a CAPA
- Reviewing/approving CAPA and recommending changes as necessary
- Completing assigned CAPA tasks and reporting the status/completion of assigned CAPA
- Reviewing and recommending changes on the overall CAPA based on review of effectiveness checks

4 DEFINITIONS/ACRONYMS

4.1 **APBMT**: Adult and Pediatric Blood and Marrow Transplant Program

4.2 **CAPA**: Corrective and Preventive Action

4.3 **CAPA Report**: Form used to document the findings of an initiated CAPA event in the MasterControl system.

4.4 **Corrective Action (CA)**: Action taken to eliminate the cause of a detected event or deviation. Corrective action is taken to prevent the recurrence of a problem. Please note that any action taken to address the cause of a problem is part of a CAPA (ex., additional training or changes to procedures, processes, or systems).

4.5 **CQP**: APBMT Clinical Quality Program

4.6 **DCS**: Document Control System

4.7 **Effectiveness Check:** Method or data used to determine the effectiveness of a CAPA.

4.8 External Reporting: The dissemination of information to an outside party as required by any applicable regulation, standard, contract, or quality agreement. This could include reporting to the FDA, an external sponsor, or another entity.

4.9 Final Quality Approval: The point in the review process after which an event/CAPA report is considered to be complete/final and in a form that may be disseminated to an outside party as a complete/final document.

4.10 **MasterControl**: An electronic 21 CFR compliant electronic data management system.

4.11 **MD**: Medical Director

4.12 **OOS**: Out of Specification

4.13 **Preventive Action (PA)**: An activity or step implemented to prevent the initial occurrence of a problem, based on an understanding of the product or process. Please note that any action taken to prevent initial occurrence of a problem is part of a CAPA (ex. additional training or changes to procedures, processes or systems)

4.14 **Root Cause**: An identified reason for the presence of a defect, problem, deviation, or nonconformity, the most basic reason which, if eliminated, would prevent recurrence. The root cause can also be defined as the source or origin of an event.

4.15 **SME**: Subject Matter Expert

4.16 **SOP**: Standard Operating Procedure

5 MATERIALS

5.1 N/A

6 EQUIPMENT

6.1 Computer access to MasterControl.

7 SAFETY

7.1 N/A

8 PROCEDURE

8.1 When an issue requiring a corrective or preventive action is identified, or otherwise deemed warranted by management, trained personnel will open a CAPA Report in MasterControl. In addition to risk-driven CAPA initiation, a CAPA may be triggered from other quality systems

8.2 All changes or actions taken to address/eliminate the root cause of a detected deviation/event should be tracked as a Corrective Action (CA) on COMM-PAS-015 FRM1 *CAPA Report*. Examples would include changes to standard operating procedures (SOPs), processes, or systems; equipment installation and/or repairs; and formal training and/or re-training.

8.2.1 Additionally, changes/actions taken to address/reduce risk, an anticipated failure, or a cause of a potential deviation should be tracked as a Preventive Action (PA) on COMM-PAS-015 FRM1 *CAPA Report.* Examples would include changes to SOPs, processes, or other systems to help prevent the occurrence of an issue.

8.2.2 It is possible that corrective or preventive actions to address an identified root cause may be temporary or require further evaluation, i.e., the action taken is not intended to be permanent but intended to gauge the impact of an action on a system. In these cases, where deviation from established procedure will be required, approved documentation is required for execution of this change to ensure that all affected personnel have the information required to execute the temporary action.

8.2.2.1 Examples of the documentation include, but are not limited to:

- Protocol
- Executable form or batch record
- Job Aid
- Work Instruction

8.2.2.2 Such documentation will be reviewed and approved by SME, Area Manager, and CQP before implementation and is a requirement to be attached to the associated COMM-PAS-015 FRM1 *CAPA Report* as part of plan approval.

8.2.2.3 CQP review also includes verification that sufficient documentation for the case outlined in section 8.1.3 is included in the CAPA plan to execute the CAPA.

8.2.2.4 Additionally, the action and effectiveness check in the CAPA plan must detail the duration for which this change will be in effect, what specific steps will be taken to evaluate the temporary change, what data will be collected, and whether at the end of the evaluation period, procedure will revert to established SOP, or revision to SOP to incorporate the change will be required.

8.2.3 If the change/action occurred during the deviation investigation and the actions are completed before closure of the associated COMM-PAS-013 FRM1 *Deviation and Investigation Report*, any actions that fulfill the requirements stated within this SOP should still be captured on COMM-PAS-015 FRM1 *CAPA Report*.

8.2.4 As defined in COMM-PAS-014 *Risk Assessment Procedure*, CAPAs may be required as an outcome of the associated risk assessments/score. All risk assessments associated with event investigations should be expanded to include potential, related outcomes that could occur in the future despite not having occurred in this specific event, so that any potential preventive actions can be evaluated and captured. To help accomplish this, a systemic view should be taken when looking at the event/issue to help determine if any changes can be made to facilitate a reduced risk of a similar event occurring in the future. If a preventive action (PA) is warranted, after completing this expanded assessment of alternative outcomes, it should be tracked as a CAPA on COMM-PAS-015 FRM1 *CAPA Report*.

8.3 Timeline for CAPA Initiation

8.3.1 A CAPA should be initiated before closure of the associated event (deviation/investigation, adverse event, complaint, OOS, etc.), risk assessment, audit finding, or related document. The CAPA will be

documented using the CAPA Report (COMM-PAS-015 FRM1). As a best practice, the CAPA Report should undergo pre-approval routing (first routing) in parallel with or around the same time as an associated event.

8.3.2 All proposed effectiveness checks for verification of CAPA, as well as projected completion dates and responsible parties, should be outlined in the applicable section of the CAPA report before initial QA and Medical Director approval for implementation. Timelines for effectiveness checks may be determined on a case-by-case basis and represent an adequate period of time sufficient to accurately gauge effectiveness. The rationale for the duration of an effectiveness check should be stated in the CAPA report.

8.4 Completing the MasterControl CAPA Report

8.4.1 Refer to Appendix A for detailed instructions on completing the sections of the CAPA Report.

8.4.2 If the initiator of a CAPA is not the Supervisor/Manager, modify step routes, as applicable, to include the Supervisor/Manager for review and approval.

8.4.3 Verify that the appropriate SMEs (e.g., individuals assigned as a responsible person to an action or effectiveness check in a CAPA), Medical/Program Director, and/or physician, as applicable, are selected for review and approval routes and modify step routes as necessary.

8.4.3.1 If a CAPA requires cross-functional collaboration for the execution of corrective/preventive actions or effectiveness checks, it is recommended that a meeting be convened before routing for plan approval to ensure alignment between functional groups on dates, actions, and content.

8.5 Review Process

8.5.1 Each CAPA route goes through the MasterControl system twice:

8.5.1.1 First Routing: Pre-approval of CAPA(s), Proposed Effectiveness Check(s) and Pre-CAPA Risk Assessment Summary.

8.5.1.2 Second Routing: Final approval of CAPA Outcome, Outcome of the Effectiveness Check(s), and the Effectiveness Check Risk Assessment Evaluation.

8.5.1.3 If anticipated timelines for the CAPA and/or the effectiveness checks are not met during the second routing, an explanation is detailed in the applicable section of the CAPA Report.

8.5.2 Upon second routing of the CAPA, for approval of the CAPA Outcome and Outcome of the Effectiveness Check, when applicable, (as detailed in Appendix A) initiators must complete an Effectiveness Check Risk

Assessment Evaluation in which initiators will reassess if the risk was reduced as a result of the implemented CAPA(s).

8.5.2.1 During this review, when applicable, initiators will address a review of any applicable risk assessments completed to ensure consideration of how the CAPA impacts already established risks, and to ensure this is factored into the determination of the effectiveness of this change and its associated risk score.

8.5.2.2 If this evaluation determines that the associated risk was not sufficiently reduced to an acceptable level, or if the associated Effectiveness Checks cannot demonstrate that the associated CAPA is effective, in consultation with CQP, additional CAPA(s) may be necessary. Additionally, initiators should evaluate within this CAPA if the identified root cause of the associated event was well defined/established, and/or if the CAPA did not address the root cause sufficiently.

8.5.3 CQP completes a detailed assessment on all submitted CAPAs for completeness, a suitable level of detail, and appropriate resolution of the original issue, when applicable.

8.5.4 CQP assesses step routing for completeness and accuracy and modifies steps as necessary to ensure thorough review.

8.5.5 CAPA Report evaluation and approval routes include: Supervisor/Manager, Operations Review, designated trained physicians, Medical/Program Director, and CQP Director, as applicable.

8.5.5.1 Reviewers may reject any route step during the evaluation and approval process to ensure consistent and accurate documentation.

8.5.6 Open CAPA Reports are monitored and discussed by CQP in a periodic event meeting. CAPA progress will be actively monitored by the CQP in a variety of mechanisms, which may include but are not limited to monthly event management tracking meetings and regular reports that are sent to the applicable Medical Directors, as applicable. These meetings and reports will highlight key statistics such as the initiation date and projected completion date.

8.6 Maintenance of Records

8.6.1 CAPA Reports and associated forms are maintained in MasterControl and are accessible for printing and review. Reports may be generated by Document Control System (DCS) or CQP upon request.

8.6.2 All records are maintained according to the associated Program's procedure(s) for Records Management or Records Retention.

9 RELATED DOCUMENTS/FORMS

9.1 COMM-PAS-013 Deviations and Investigations

9.2 COMM-PAS-013 FRM1 Deviation and Investigation Report

9.3 COMM-PAS-015 FRM1 CAPA Report

9.4 COMM-PAS-014 Risk Assessment Procedure

9.5 COMM-PAS-006 Product Complaint Management

9.6 STCL-QA-007 Non-Conforming Products – Receipt, Processing, Distribution, and Disposition

10 REFERENCES

10.1 21 CFR 211.22(a) – Responsibilities of a Quality Control Unit

10.2 21 CFR 211.100 – Written Procedures; Deviations

10.3 21 CFR 1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products

10.4 FACT-JACIE International Standards for Cellular Therapy; Current Edition

10.5 FACT Common Standards for Cellular Therapies; Current Edition

11 REVISION HISTORY

Revision No.	Author	Description of Change(s)
01	M. Christen	• New document

Appendix A

Instructions for completing *COMM-PAS-015 FRM1 CAPA Report*

- Complete the CAPA Report, filling in all required information.
- Record N/A in any field that does not apply.
- Note: The CAPA routes twice. Initially for pre-approval of CAPA(s) and Proposed Effectiveness Check(s) (first routing) and a second time for the Outcome of the CAPA and Effectiveness Check(s) (second routing).

Section	Instructions
CAPA Report Number	CAPA Report number is auto-populated by Master Control.
CAPA Report Initiated By:	This field is auto-populated by MasterControl to indicate which user initiated the CAPA Report.
Date Initiated	This field is auto-populated by MasterControl to indicate what date the CAPA Report was initiated.
Tab 1: CAPA Summary Tab	
Program	Select applicable program for which the CAPA pertains.
Event Report(s) associated with this CAPA	Enter the report number(s) that resulted in this CAPA report (ex. Deviation/Investigation, Risk Assessment Report, AE, Complaint).
Issue Statement	Summarize the issue **and** root cause of the issue being addressed by this CAPA. Please remember that this CAPA may be routing months after the original event. ***Note:*** *Although the entire event does not need to be summarized again, please provide enough details that anyone could generally understand the situation.*
CAPA and EC – 1, 2, 3 Tab	
Corrective Actions (Pre-Approval Routing/First Routing)	**For pre-approval (First Routing) of the CAPA report:** If the CAPA is corrective, list all Corrective Actions (measures to correct the cause of the issue and prevent recurrence). Select appropriate toggle to indicate if action is corrective. • Add projected completion date • Add initials of responsible person ***Note:*** *If the action is intended to be temporary, detail must be included on the intended duration and steps to be taken following the implementation/evaluation period. Additionally, CAPA plan must include documentation as detailed in Step 8.1.3.1 above (I.e. protocol, Job Aid, executable form or batch record, or work instruction), to detail exact steps to be taken to execute the temporary action.* ***Note:*** *the evaluation period for any temporary change will not begin until there is approval, including the CAPA owner and Quality Assurance, of the documentation to be used to implement the temporary change.*

Section	Instructions
	Note: *As a best practice, the CAPA Report should undergo pre-approval routing in parallel with or around the same time as the associated event.*
Preventive Actions (Pre-Approval Routing/First Routing)	**For pre-approval (First Routing) of the CAPA report:** If the CAPA is preventive, list all Preventive Actions (action to eliminate the cause of a potential issue). Select appropriate toggle to indicate if action is preventive. • Add projected completion date • Add initials of responsible person ***Note:*** *If the action is intended to be temporary, detail must be included on the intended duration and steps to be taken following the period, and also must include documentation to detail exact steps to be taken to execute the temporary action.* ***Note:*** *As a best practice, the CAPA Report should undergo pre-approval routing in parallel with or around the same time as the associated event.*
Change Control Request(s) associated with this CAPA (Second Routing)	Include any change control request number(s) that were associated with changes from this CAPA report. ***Note:*** *May be populated if known at time of pre-approval/first routing but required to be populated at time of second routing.*
CAPA Outcome (Final/Second Routing)	**For final approval (Second Routing) of the CAPA report:** After completion of the CAPA and effectiveness checks, describe the outcome of the CAPA(s). For example, what was implemented and when was the associated document or process implemented? • Add date completed (in associated Corrective and Preventive Actions Box) and describe outcome of Corrective or Preventive Action(s). Date should match any documented dates described in text and/or attachments; If not, explain in text. • If projected Corrective or Preventive Action(s) date is not met, please explain why completion was delayed and evaluate if there is any impact due to the delay.
Proposed Effectiveness Checks (Pre-Approval/First Routing)	**For pre-approval (First Routing) of the CAPA report:** To be populated during first routing with proposed Corrective or Preventive Action(s). List all Proposed Effectiveness Checks (measures to verify effectiveness of CAPA). • Add projected completion date • Add initials of responsible person • Each CAPA should have an appropriate Effectiveness Check. • The rationale for the duration of an effectiveness check should be stated. • If any additional actions are required (such as actions taken following a temporary corrective action), steps to be taken to implement the temporary action into procedure, or to revert to established procedure must be included.

Section	Instructions
Effectiveness Check Outcome (Final/Second Routing)	**For final approval (Second Routing) of the CAPA report:** When the CAPA routes for the final (second) time, describe the effectiveness check outcome in the associated box. For example, what occurred during the effectiveness check and did it indicate the CAPA was effective? If not, describe and/or formulate additional CAPA and/or effectiveness checks for existing CAPA. A new CAPA will likely be needed if effectiveness was not demonstrated. If there were any changes made from the original proposal, please explain those and detail why the effectiveness check is still adequate and appropriate for the CAPA. • Add date completed (in associated Effectiveness Checks Box) • If projected EC date is not met, please explain why completion was delayed and evaluate if there is any impact due to the delay. **Note:** The effectiveness check(s) should demonstrate full resolution of the problem with no repeat occurrences of the same type of incident. If this cannot be demonstrated, then a new CAPA may be needed.
Risk Assessment Tab	
Pre-CAPA Risk Assessment Summary (First Routing)	For CAPAs generated as a result of an event (deviation/investigation, complaint, etc.) or where a risk assessment was completed per scoring in *COMM-QA-077 Risk Assessment Procedure*, populate details of the original Risk Assessment associated with this CAPA. • Include the scores associated with each risk assessment parameter and the corresponding combined risk assessment score.
Effectiveness Check Risk Assessment Evaluation (Second Routing)	When the CAPA routes for the final (second) time, use this section to document a reevaluation of the original Risk Assessment associated with this CAPA. Summarize the overall risk assessment outcome after implementation of associated CAPA(s). • Include a reassessment of each risk assessment parameter and associated score • Clearly address if risk was reduced after implementation of CAPAs and if effectiveness and acceptable level of risk demonstrated.
External Reporting / Attachments Tab	
External Reporting	Use this section to document the determination of any need for regulatory or other external reporting to vendors/sponsors, per applicable quality agreements. If notification is required in advance of closing the CAPA, documentation, such as email, FAX etc. should be attached to the document in the Attachments section. This section to be populated by author/initiator if known at time of report and/or QSU at time of review.
Attachments	Use this section to attach all applicable documents.
Appendix Tab	

Section	Instructions
Appendix from COMM-PAS-015	The Appendix from *COMM-PAS-015 Corrective and Preventive Actions* is attached for easy reference.

Signature Manifest

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COMM-PAS-015 Corrective and Preventive Actions

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