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

DOCUMENT NUMBER: COMM-PAS-018

DOCUMENT TITLE:
Clinical Quality Program (CQP) Audit Procedure

DOCUMENT NOTES:

Document Information

Revision: 01	**Vault:** COMM-PAS-rel
Status: Release	**Document Type:** COMM-PAS

Date Information

Creation Date: 20 Jun 2025	**Release Date:** 01 Jul 2025
Effective Date: 01 Jul 2025	**Expiration Date:**

Control Information

Author: MC363	**Owner:** MC363
Previous Number: None	**Change Number:** PAS-CCR-043

COMM-PAS-018
APBMT Clinical Quality Program (CQP) Audit Procedure
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1 PURPOSE

1.1 To define the procedure for performing internal quality audits, facility qualification audits, facility requalification audits, and supplier qualification audits, where the Adult and Pediatric Blood and Marrow Transplant Program (APBMT) Clinical Quality Program is responsible for overseeing quality functions.

2 INTRODUCTION

2.1 The APBMT Clinical Quality Program (CQP) is required by the Code of Federal Regulations (CFR), current Good X Practices (cGXP), and several accreditation agencies to conduct independent examinations to ensure that Quality Management Systems' (QMS) processes are being followed and are functioning effectively within established procedures, regulations, and guidance documents.

2.2 A well-organized and efficient audit program captures the pulse of a cellular therapy organization's operations and is also the best line of defense against deficiencies found by external agencies.

3 SCOPE AND RESPONSIBILITIES

3.1 This procedure applies to all programs/processes where the APBMT CQP is responsible for quality oversight and to the audits used for internal quality assessment, used to qualify or requalify suppliers when deemed necessary, and used to qualify/requalify facilities.

3.2 CQP personnel involved in planning, conducting, or reporting quality audits are responsible for this Standard Operating Procedure (SOP)'s compliance and training. The CQP Director and/or designee is responsible for ensuring initial and ongoing training of CQP personnel.

3.3 The CQP Director and/or designee is responsible for communicating with applicable Division Chiefs, Program and/or Facility Medical Directors, and applicable staff when planning and reporting the results of an internal audit.

3.4 Staff involved in the audits are responsible for complying with the requirements of this SOP.

3.5 Division Chiefs and Program and/or Facility Medical Director(s) are responsible for ensuring that quality standards for their respective programs and facilities comply with the principles of this SOP.

4 DEFINITIONS/ACRONYMS

4.1 APBMT Adult and Pediatric Blood and Marrow Transplant Program

4.2 CAPA Corrective and Preventive Action

4.3 CFR Code of Federal Regulations

4.4 cGXP: Current Good X Practices. Encompasses all current Good (manufacturing, clinical, laboratory, tissue, etc.*)* practices to maintain quality of the process/product.

4.5 Control: Demonstrating continued safety, purity, and potency of the product, compliance with applicable product and establishment standards, and compliance with cGXP.

4.6 Critical Observation: A finding of a confirmed deficiency that requires immediate attention and/or intervention that affect SQIPP (Safety, Quality, Identity, Potency, and Purity) and/or reporting to external agencies.

4.7 CQP APBMT Clinical Quality Program

4.8 Deviation: An unplanned or planned variance from a standard operating procedure (SOP) or other controlled document specified process.

4.9 External Audit/Inspection: Conducted by agencies or organizations (e.g. FACT, FDA) independent of the program being audited/inspected.

4.10 FACT Foundation for the Accreditation of Cellular Therapy

4.11 FDA Food and Drug Administration

4.12 IEC Immune Effector Cell

4.13 Lead Auditor: The auditor most responsible for managing the audit, verifying the accuracy of audit related documents, and tracking related audit progress.

4.14 Major Observation: A finding of a confirmed deficiency that is considered to be significant and may have a negative impact on the product, deliverable, service or contractual obligation. Repeated minor observations may also constitute a major observation, particularly when they indicate a more significant or systemic problem.

4.15 Minor Observation: A finding of a confirmed deficiency that does not necessarily have a negative impact on the product, deliverable, service, or contractual obligation.

4.16 QA: Quality Assurance - QA provides information regarding levels of performance that can be used in setting priorities for process improvement. QA includes retrospective review and analysis of operational performance data to determine if the overall process is in a state of control and to detect shifts or trends that require attention.

4.17 QC: Quality Control - QC provides feedback to operational staff about the state of a process that is in progress. Product QC is performed to determine whether the product or service meets specifications.

4.18 QI: Quality Improvement - QI is intended to attain higher levels of performance either by creating new or better features that add value or by removing existing deficiencies in the process, product, or service. Observations do not require a written response, deviation, or CAPA, but should be discussed and considered.

4.19 QMS Quality Management System

4.20	SME	Subject Matter Expert
4.21	SOP	Standard Operating Procedure
4.22	SQIPP	Safety, Quality, Identity, Potency, and Purity
4.23	STCL	Stem Cell Laboratory
4.24	TED	Transplant Essential Data

5 MATERIALS

5.1 N/A

6 EQUIPMENT

6.1 N/A

7 SAFETY

7.1 The CQP will comply with Universal Precautions implemented for each program or facility audited to uphold established requirements.

8 PROCEDURE

8.1 Audit Team

8.1.1 The audit team consists of a CQP lead auditor and designated APBMT and Stem Cell Laboratory (STCL) auditor independent of the process being audited, however, has sufficient knowledge in the process, as needed. Subject matter experts (SMEs) will be asked to join the audit team for further expertise, as needed, and may lead content review, as applicable. The CQP is responsible for scheduling the audit and evaluating the number of resources needed based on the type and complexity of the audit being performed.

8.2 Audit Frequency

8.2.1 The CQP will typically perform routine internal audits on the QMS processes applicable to each program and/or facility once during each calendar year.

8.2.1.1 The audit period (time frame) will be based on the COMM-PAS-018 JA1 *CQP Audit Schedule for APBMT and STCL*.

8.2.2 The CQP may conduct internal audits with more frequency based upon observations from previous audits or unexpected events, or concerns.

8.2.3 Facility qualification/requalification will be performed as needed and as appropriate to the program and/or facility.

8.2.4 Supplier qualification audits will be performed based upon the outcome of the supplier assessment made in accordance with COMM-PAS-017 *Supplier Qualifications.*

8.3 Focus of QMS Process Audits

8.3.1 The CQP will conduct audits on the follow QMS processes, where applicable.

8.3.1.1 Personnel/Training

8.3.1.2 Facilities

8.3.1.3 Environmental Monitoring

8.3.1.4 Equipment Management

8.3.1.5 Inventory Control/Supply Management

8.3.1.6 Document Control/Record Management

8.3.1.7 Process Management and Control

8.3.1.8 Product Release

8.3.1.9 Event Management, such as effectiveness of CAPA

8.3.2 For the STCL and APBMT, the CQP will also conduct audits on the following QMS processes.

8.3.2.1 Accuracy of clinical data

8.3.2.2 Accuracy of Transplant Essential Data (TED) forms

8.3.2.3 Donor Management

8.3.2.3.1 Donor screening and testing

8.3.2.3.2 Interim Assessment of donor suitability and eligibility before the start of the procedure

8.3.2.3.3 Donor eligibility determination before the start of the procedure

8.3.2.4 Management of Cellular Therapy Products with Positive Microbial Cultures

8.3.2.5 Immune Effector Cell (IEC) Therapy Safety Endpoints and Toxicity Management

8.3.2.6 Supplier/Third-Party Qualification

8.3.2.7 Chemotherapy Records and Prescription Ordering System against the Protocol

8.4 Scheduling the Audit

8.4.1 The CQP will notify, in writing, the program/process designee about the need to conduct an audit and will work with the designee to determine an acceptable timeframe. The receiving program/process designee is asked to acknowledge receipt of the audit notification within 2 business days.

8.4.2 Audits may also be conducted without prior or with limited notification if deemed warranted by the CQP.

8.4.3 The program/process staff will make accessible to the auditor(s) all records, equipment, facilities, and applicable personnel involved with the program/process as appropriate to the scope of the audit.

8.5 Conducting the Audit

8.5.1 The audit team conducts an opening meeting with the program and/or facility staff to review the objective and scope of the audit.

8.5.2 The audit team will conduct the audit and may ask for copies of documentation to attach to the final audit report.

8.5.3 Any issues found during an audit that may affect the integrity of ongoing activities will be brought to the attention of the CQP Director and applicable personnel.

8.5.4 Auditors will maintain the confidentiality of the audit and will only discuss outcomes of the audits with appropriate personnel.

8.6 Audit Report

8.6.1 COMM-PAS-018 FRM1 *Internal CQP Quality and Process Audit Report*, which is a template that can be modified to fit any number of observations.

8.6.2 COMM-PAS-018 FRM5 *Supplier Qualification Audit Report* is used to report in-place QMS at the Supplier's organization.

8.6.3 COMM-PAS-018 FRM3 *APBMT Chemotherapy and Treatment Plan Audit Report* is used as a guide when conducting audits on the chemotherapy records and prescription ordering system against the protocol.

8.6.4 COMM-PAS-018 FRM6 *Internal Quality Systems Facility Qualification/Requalification Audit Report* is used when conducting audits on the chemotherapy records and prescription ordering system against the protocol.

8.6.5 COMM-PAS-018 FRM4 *APBMT IEC Therapy Safety Endpoints and Toxicity Management Audit Report* is used as a guide when conducting the IEC therapy safety endpoints and toxicity management audit.

8.6.6 COMM-PAS-018 FRM2 APBMT *Transplant Essential Data (TED) Form Audit Report* is used when conducting the TED form audit.

8.7 Audit Observations and Classifications

8.7.1 Documentation of the audit observations will be detailed, concise, and accurate.

8.7.2 The lead auditor ensures that the documented observations on the report are accurate and within the scope of the audit.

8.7.3 The lead auditor and CQP Director or designee will sign the audit report before distributing it to the representative(s) of the audited program and/or facility.

8.7.4 Internal observations are classified as Critical, Major, or Minor

8.7.5 A **Critical Observation** is a finding that affects the Safety, Quality, Identity, Potency, and Purity (SQIPP). Thus, it requires immediate attention or intervention and/or reporting to external agencies.

8.7.5.1 In situations with Critical Observations, the lead auditor will notify the CQP Director or designee, and the Program and/or Facility's Medical Director and Management immediately.

8.7.5.2 Critical observations may include but are not limited to those that:

8.7.5.2.1 Compose a threat against the life, health, or rights of patients or study subjects.

8.7.5.2.2 Pose a threat to employee safety.

8.7.5.2.3 May result in the severing of a contractual service agreement, loss of business, or assumed liability.

8.7.5.2.4 May result in regulatory, civil or criminal sanctions and/or penalties.

8.7.5.3 In situations with Critical Observations, the lead auditor will notify the CQP Director or designee, and the Program and/or Facility's Medical Director and Management immediately.

8.7.6 A **Major Observation** is a finding of a confirmed deficiency or non-compliance that is considered to be significant and may have a negative impact on the product, deliverable, service or contractual obligation. Major observations may include but are not limited to those that:

8.7.6.1 Jeopardize the integrity of data.

8.7.6.2 Substantially reduce process quality and impede deliverable(s)/outcome(s).

8.7.6.3 Indicate the absence or breakdown of an element in the quality management system.

8.7.7 A **Minor Observation** is a finding that does not necessarily have a negative impact on the product, deliverable, service, or contractual obligation, and/or any observation with a single or low frequency of occurrence that does not meet the criteria of a Major Observation.

8.7.8 Repeated Minor Observations may be escalated to a Major Observation, particularly when they indicate a more significant or systemic problem.

8.7.9 Remediation actions will be documented by the audit designee in the response section of the COMM-PAS-018 FRM1 *Internal CQP Quality and Process Audit Report*. The responses will be reviewed by the lead auditor for appropriateness prior to closing the audit.

8.7.10 Remediation actions for observations labelled as Critical or Major must be verified by the lead auditor as being effective prior to closing the audit.

8.7.11 Remediation actions for observations labelled as Minor do not have to be verified prior to closing the audit.

8.7.12 Depending on the type and severity of the audit finding, further investigation and remediation actions may need to be documented per COMM-PAS-013 *Deviations and Investigations* and COMM-PAS-014 *Risk Assessment Procedure*. If needed, the CQP and/or lead auditor will work with the audit designee to ensure that a complete investigation has been performed and documented.

8.7.13 In the event that a CAPA is needed, documentation of the CAPA and the effectiveness of the CAPA will be performed and documented per COMM-PAS-015 *Corrective and Preventive Actions*.

8.7.14 COMM-PAS-018 FRM5 *Supplier Qualification Audit Report* observations do not have to be classified as Critical, Major, or Minor since observations are solely utilized in determining whether the Supplier is acceptable for use or continued use. However, all observations must be discussed and a remediation plan documented in consultation with the Supplier prior to approval. CQP reserves the option not to approve the supplier based on the nature of the observation or the remediation action plan.

8.7.15 Observations discovered during site qualification or requalification using the COMM-PAS-018 FRM6 *Internal Quality Systems Facility Qualification/Requalification Audit Report* will not be documented as Critical, Major or Minor, but must be discussed and a remediation plan documented prior to the site opening or continuing operations. In situations where a site provides written responses and a remediation plan that is in process, the site may still open or continue operations.

8.7.16 Observations discovered during the APBMT chemotherapy and treatment plan audit, using the COMM-PAS-018 FRM3 *APBMT Chemotherapy and Treatment Plan Audit Report* or APBMT IEC therapy safety endpoints and toxicity management audit, using the COMM-PAS-018 FRM4 *APBMT IEC Therapy Safety Endpoints and Toxicity Management Audit Report,* will not be documented as Critical, Major, or Minor, but all the appropriate resolutions to any discrepancies must be remediated before closing the audit.

8.8 Audit Scoring and Audit Plan

8.8.1 Internal audits will receive a composite score of either Excellent, Satisfactory, Needs Improvement, or Fail based on the number of Minor, Major, or Critical Observations.

8.8.2 The following table describes how each internal audit will be scored.

Score	Minor	Major	Critical	Audit Plan
Excellent	≤5	0	0	Re-audit – **12-MONTH** period

Satisfactory	>5	0	0	Re-audit – **12-MONTH** period
Needs Improvement	Any	1	0	Re-audit – **12-MONTH** period
Fail	Any	>1	Any	Complete re-audit within 6 months

8.8.3 COMM-PAS-018 FRM5 *Supplier Qualification Audit Report* and the COMM-PAS-018 FRM6 *Internal Quality Systems Facility Qualification/Requalification Audit Report* will not receive a composite score but will only be documented as "approved for use/continued use" or "not approved for use/continued use".

8.9 Audit Receipt and Responses

8.9.1 The audit draft recipient should receive the audit report from CQP within 30 calendar days of the last day of the audit. If this is not feasible, the recipient should be notified within the 30-day window of the audit delay and the estimated date of completion. The recipient is asked to acknowledge receipt of the audit report via email within five (5) business days.

8.9.2 If audit responses are needed, responses should be returned to CQP within 30 calendar days of receiving the audit report. If this is not feasible, CQP should be notified within the 30-day window so that agreement can be reached on when the responses may be received.

8.9.2.1 NOTE: The remediation action does not need to be completed within 30 calendar days; however, a remediation plan must be described in the response.

8.9.3 The type of response will be dependent upon the observations observed. CQP will work with the audit draft recipient in determining the most appropriate response to the observation.

8.10 Audit Closure

8.10.1 Once the audit responses have been reviewed and approved by CQP as required above based on the audit findings, the audit will be closed.

8.10.2 Completed audit documentation will be retained by the CQP.

9 RELATED DOCUMENTS/FORMS

9.1 COMM-PAS-017 Supplier Qualifications

9.2 COMM-PAS-013 Deviations and Investigations

9.3 COMM-PAS-015 Corrective and Preventive Actions

9.4 COMM-PAS-014 Risk Assessment Procedure

9.5 COMM-PAS-018 FRM1 Internal CQP Quality and Process Audit Report

9.6 COMM-PAS-018 FRM5 Supplier Qualification Audit Report

9.7 COMM-PAS-018 FRM6 Internal CQP Facility Qualification/Requalification Audit Report

9.8 COMM-PAS-018 FRM3 APBMT Chemotherapy and Treatment Plan Audit

9.9 COMM-PAS-018 FRM4 APBMT IEC Therapy Safety Endpoints and Toxicity Management Audit Report

9.10 COMM-PAS-018 FRM2 APBMT Transplant Essential Data (TED) Form Audit Report

10 REFERENCES

10.1 21CFR Parts 600 - 680, Biological Products

10.2 21CFR Part 1271 Current Good Tissue Practice

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

10.4 FACT Common Standards for Cellular Therapies; Current Edition

11 REVISION HISTORY

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

Signature Manifest

Document Number: COMM-PAS-018 **Revision:** 01
Title: Clinical Quality Program (CQP) Audit Procedure
Effective Date: 01 Jul 2025

All dates and times are in Eastern Time.

COMM-PAS-016 FRM1--COMM-PAS-018

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Document Release

Name/Signature	Title	Date	Meaning/Reason
Amy McKoy (ACM93)	Document Control Specialist	30 Jun 2025, 05:37:16 PM	Approved