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

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**DOCUMENT TITLE:**
Risk Assessment Procedure

**DOCUMENT NOTES:**

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# COMM-PAS-014
# Risk Assessment Procedure

## 1 PURPOSE

1.1 The purpose of this procedure is to describe the assessment of risk and resulting mitigation activities/control actions for change controls and applicable events, including but not limited to Deviations/Investigations, Corrective and Preventive Action (CAPA), and Product Complaints.

## 2 INTRODUCTION

2.1 A risk assessment (RA) system is necessary to adequately assess the potential impact of a change or event, as well as what, if any, additional actions may be necessary to effectively address and/or monitor the risk.

## 3 SCOPE AND RESPONSIBILITIES

3.1 This procedure is referenced when assessing risk for change controls and events associated with the Stem Cell Laboratory (STCL) and the Adult and Pediatric Blood and Marrow Transplant Program (APBMT).

3.2 A supplemental risk assessment and associated report, separate from the matrix described here, may be deemed necessary for a number of reasons, including, but not limited to, a situation where a different tool/method is needed to assess risk than what is outlined in the current, applicable quality system, the change requires a more extensive assessment than can be captured in the change control form alone, or to evaluate a system or trend that needs a comprehensive risk assessment consisting of a Subject Matter Expert (SME) team.

3.3 Responsibilities for assessing risk are shared among all staff involved in writing or reviewing Change Controls, CAPAs, Deviations/Investigations, and other events, such as Complaints. Approval of any associated risk assessment is implicit with electronic signatures in MasterControl. Section 3.4 below details specific responsibilities for the different aspects of risk assessment.

3.4 Responsibilities

3.4.1 Operations

3.4.1.1 Operations is responsible for:

- Participating in risk management assessments and discussions.
- Identifying SMEs and providing expert input on risk assessment.
- Participating in determining if any external reporting is required to outside vendors/sponsors of events that may impact products related to their organization.

3.4.2 APBMT Clinical Quality Program (CQP)

3.4.2.1 CQP is responsible for:

- Participating in risk management assessments and discussions.

- Maintaining this risk management procedure.
- Facilitating risk assessment activities.
- Determining if any external reporting is required to outside vendors/sponsors of events that may impact products related to their organization.

3.4.3 Medical Director (MD)

3.4.3.1 The Medical Director is responsible for:

- Participating in risk management assessments and discussions.

3.4.4 Subject Matter Experts (SME)

3.4.4.1 Subject Matter Experts are responsible for:

- Participating in risk management assessments and discussions as needed based on their expertise in the product and topic of evaluation.

3.4.5 Executive Management (Division Chiefs and Quality Director)

3.4.5.1 Executive Management is responsible for:

- Governing the risk management process by providing the necessary resources, communicating risk assessment results to the organization, as applicable, and periodically reviewing risk control plan progress and effectiveness.
- Reviewing and approving additional resources that may be requested.

## 4 DEFINITIONS/ACRONYMS

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

4.2 **CAPA** Corrective and Preventive Action

4.3 **CQP** APBMT Clinical Quality Program

4.4 **DCS** Document Control System

4.5 **Detectability:** The ability to discover or determine the existence, presence, or fact of a hazard.

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

4.7 **MD** Medical Director

4.8 **Probability:** The likelihood of something happening or being the case.

4.9 **Risk:** The combination of the probability of occurrence (Rate of Occurrence and/or Likelihood of Recurrence) of harm, the impact (Risk Severity) of that harm, and the detectability of the associated hazard.

4.10 **Risk Management:** A systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring the risk.

4.11 **STCL** Stem Cell Laboratory

4.12 **Severity:** A measure of the possible consequences of a hazard.

4.13 **SQIPP** Safety, Quality, Identity, Potency, Purity of a product.

## 5 MATERIALS

5.1 Supporting reports/documents, if applicable

## 6 EQUIPMENT

6.1 Computer access to MasterControl

## 7 SAFETY

7.1 N/A

## 8 PROCEDURE

8.1 Risk Matrix

8.1.1 As part of change controls, deviations/investigations, applicable events, and risk assessments reports on three parameters, severity, probability, and detectability, which are required in order to assess risk consistently and effectively.

8.1.2 Tables 1-3 describe and define the three parameters in a 5-point scale that should be used to identify a risk score within an applicable change control, CAPA, event, or investigation. The score assigned to each parameter, as well as the rationale for the assigned score, are captured on the applicable forms (ex., Change Control Request Form, Deviation and Investigation Report, Complaint).

8.1.3 Table 4 is a summary of recommended actions for categories of overall risk scores. The recommended actions in Table 4 are generalized to account for combinations of potential scenarios. The more specific guidelines in Sections 8.1.4 and 8.2 should be followed to determine whether a CAPA and/or Change Control Request Effectiveness Check are recommended or required.

**Table 1: Severity Risk Matrix**

| S | Severity | Definition | Anticipated Harm to the Patient | GMP Non-compliance | Impact on Product |
|---|---|---|---|---|---|
| **1** | Negligible | Insignificant | None | None | No perceived impact on product |
| **2** | Marginal | At the outer or lower limits, minimal for requirements | Minimal | Minor | Unlikely impact on product, SQIPP not likely to be affected |
| **3** | Moderate | Within reasonable limits, transient or persistent | Transient or persistent, not life-threatening | Significant | May indirectly impact product quality/SQIPP |
| **4** | Serious | Very important | Permanent, life-threatening | Major | High likelihood of impacting product quality/SQIPP |
| **5** | Critical | Abnormal, unstable, unfavorable | May cause or contribute to death | Serious | Evidence of Product Impact, SQIPP affected |

**Table 2: Probability Risk Matrix**

| P | Probability | Definition (Occurrence) | Definition (Recurrence) |
|---|---|---|---|
| 1 | Rare | Not likely to happen, nearly impossible | Extremely unlikely to recur |
| 2 | Low | Occurrence is hardly likely, but possible | Unlikely to recur |
| 3 | Occasional | May occur sometimes | Likely to recur sometimes |
| 4 | Probable | Repeated occurrence, high likelihood of occurrence | Recur at a moderate rate |
| 5 | Frequent | Will happen for certain, a regularly observed event | Likely to recur regularly |

**Table 3: Detectability Risk Matrix**

| D | Detectability | Definition | Examples |
|---|---|---|---|
| **1** | High | Control system in place; automated detectability is certain | An automatic detection system that is a direct measure of the failure |
| **2** | Good | A control system is in place with a high probability of detecting the issue or its effects | SOP-driven process that facilitates a direct measure of the failure |
| **3** | Moderate | A control system in place could detect the issue or its effects | SOP-driven process that is NOT directly measuring or assessing the failure |
| **4** | Fair | Control system in place with a low probability of detecting the issue or its effects | Non-SOP driven process for the detection of direct measures of the failure |
| **5** | Low | No control system is in place to detect the issue. | No ability to detect the failure, or no SOP-driven process to indirectly detect the failure |

**Table 4: Overall Risk Scores (Ranges) and Recommended Actions**

| ***Risk Score (Severity Multiplied by Probability Multiplied by Detectability)*** | ***Recommended Action*** |
|---|---|
| 1-25 | Evaluate the current controls and determine whether additional efforts can be made to bring the risk as low as reasonably possible. |
| | **Event:** Likely, events associated with this risk score profile are not significant enough to require CAPAs. Therefore, CAPAs are optional, but one would be strongly recommended if one risk parameter (severity/probability/detectability) is scored a 5 and CAPA is feasible for the root cause identified. If one risk parameter is scored a 5 and no CAPA is launched, justification will be required within the associated event.<br>**Change Control:** Likely, changes associated with this risk score profile are not significant enough to require effectiveness checks; therefore, no effectiveness check is required. However, effectiveness checks are recommended if one risk parameter (severity/probability/detectability) is scored a 5. If one risk parameter is scored a 5 and no effectiveness check is completed, justification will be required within the associated change control. |
| 26-50 | Evaluate the current controls and determine whether additional efforts can be made to bring the risk as low as reasonably possible. |
| | **Event:** CAPAs are optional but recommended if one risk parameter (severity/probability/detectability) is scored a 5, and CAPA is feasible for the root cause identified. If one risk parameter is scored a 5 and no CAPA is launched, justification will be required within the associated event.<br>**Change Control:** No effectiveness check is required, but recommended if one risk parameter (severity/probability/detectability) is scored a 5. If one risk parameter is scored a 5 and no effectiveness check is completed, justification will be required within the associated change control. |
| 51-75 | Additional effort should be considered to bring risk as low as reasonably possible and/or to an acceptable level. |
| | **Event:** CAPAs are optional but recommended if one risk parameter (severity/probability/detectability) is scored a 5, and CAPA is feasible for the root cause identified. If one risk parameter is scored a 5 and no CAPA is launched, justification will be required within the associated event.<br>**Change Control:** No effectiveness check is required, but recommended if one risk parameter (severity/probability/detectability) is scored a 5. If one risk |

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| | parameter is scored a 5 and no effectiveness check is completed, justification will be required within the associated change control. |
| 76-100 | Additional efforts should be made to reduce the risk to as low as reasonably possible and to an acceptable level. |
| | **Event:** CAPA Mandatory<br>**Change Control:** Effectiveness Check Mandatory |
| 101-125 | Additional efforts are required to reduce the risk to as low as reasonably possible and to an acceptable level. |
| | **Event:** CAPA Mandatory<br>**Change Control:** Effectiveness Check Mandatory |

**Note:** Within an event investigation/report, risk assessments 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 appropriately as a CAPA. To 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. The risk score and rationale should reflect this "what if"/future assessment to ensure risk has been assessed most completely.

8.1.4 Once the risk assessment is performed in change controls, deviations/investigations, and applicable events, evaluate the need for a CAPA and Change Control Request Effectiveness Check based on the criteria listed in Table 4 above for combined scores. Additionally, requirements and recommendations for CAPAs based on certain individual risk scores in severity, probability, and detectability are outlined below. If CAPA and Change Control Request Effectiveness Check are required or recommended and not performed (e.g., because CAPA was not feasible), justification must be documented.

8.1.4.1 CAPA for Deviations and/or Effectiveness Check for Change Control **are required** if:

8.1.4.1.1 The total combined score is >75.

8.1.4.1.2 The score selected for Severity suggests significant risk to patient safety (i.e., 4 [permanent, life threatening], or 5 [may cause or contribute to death]).

8.1.4.2 CAPA for Deviations and/or Effectiveness Check for Change Controls **are recommended** if:

8.1.4.2.1 The total combined score is between 26-75 or

8.1.4.2.2 The score selected for Severity is a 4 (permanent, life-threatening)

8.1.4.2.3 The score selected for Probability is a 5 (Will happen for certain, a regularly observed event)

8.1.4.2.4 The score selected for Detectability is a 5 (no control system in place to detect the issue)

8.1.4.3 If none of the conditions listed above are met and the combined score is ≤25 in the risk assessment, risk-driven CAPA and/or Effectiveness Check for Change Control are optional, unless required by SOP requirements detailed in COMM-PAS-013 *Deviations and Investigations* and/or

COMM-PAS-004 *Change Control*, and that decision must be documented in the event or change control record in the risk assessment section. However, the goal is to always work to bring the risk as low as reasonably possible.

8.2 Risk Evaluation

8.2.1 Trained personnel, when completing and/or reviewing applicable MasterControl documentation, will use the three required parameters, severity, probability, and detectability (Tables 1-3), to evaluate risk and determine any potential requirements for additional actions.

8.2.2 With this risk assessment methodology, each parameter, severity, probability, and detectability will be scored individually 1-5 based on definitions and examples in Tables 1-3 above.

8.2.3 The scores of each parameter will then be multiplied to generate a final risk score for the event or change. Explanations and/or rationale for the determined score will be required for each parameter within a deviation/investigation, complaint, change control, or other document as described. When assessing risk within one parameter, if two scores are determined (such as severity on product vs patient), the more stringent (higher score) assessment will be used when calculating the final risk score, and the requirements detailed in 8.1.3 will apply. Rationale for the lower score should also be provided in the associated Deviation/Investigation, Complaint, or Change Control.

8.2.3.1 Within an event investigation/report, risk assessments 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 appropriately as a CAPA. To 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. The risk score and rationale should reflect this “what if”/future assessment to ensure risk has been assessed most completely. Additionally, if a single risk matrix attribute is scored 5 and no CAPA is launched, justification for the determination that a CAPA is not necessary will be required within the associated event. See Table 4.

8.2.3.2 Within a change control form, risk assessments should be conducted to help determine if any additional supporting work or documentation is needed to support the change or if an effectiveness check should be conducted following implementation of the change, as detailed in Table 4. Additionally, if a single risk matrix attribute is scored 5 and no effectiveness check is deemed necessary, justification will be required within the associated event.

8.3 Maintenance of Records

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

## 9 RELATED DOCUMENTS/FORMS

9.1 COMM-PAS-004 Change Control

9.2 COMM-PAS-006 Product Complaint Management

9.3 COMM-PAS-006 FRM1 Product Complaint Form

9.4 COMM-PAS-004 FRM1 Change Control Request (Effectiveness Check)

9.5 COMM-PAS-004 FRM2 Change Control Request (No Effectiveness Check)

9.6 COMM-PAS-013 Deviations and Investigations

9.7 COMM-PAS-015 Corrective and Preventive Actions

9.8 COMM-PAS-015 FRM1 CAPA Report

9.9 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 Hematopoietic Cellular Therapy Product Collection, Processing, and Administration; Current Edition

10.5 FACT Common Standards for Cellular Therapies; Current Edition

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