STANDARD OPERATING PROCEDURE

OBJECTIVE/SCOPE

To establish procedures for reporting unanticipated problems involving risks to participants or others (UPs).

MATERIALS

1. NMDP IRB Reportable Event Form

SAFETY

Not applicable

DEFINITIONS

1. **10-CBA protocol:** NMDP study titled, *A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs) for transplantation in pediatric and adult patients with hematologic malignancies and other indications*

2. **Adverse event:**

   2.1. *Defined by the Office of Human Research Protections (OHRP)* as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

   2.2. *Defined by the Food & Drug Administration (FDA)* as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

3. **Blood and Marrow Transplant Clinical Trials Network (BMT CTN):** A network sponsored by the National Institutes of Health (NIH) that conducts large multi-institutional clinical trials addressing important issues in hematopoietic cell transplantation thereby furthering understanding of the best possible treatment approaches.

4. **Center for International Blood and Marrow Transplant Research (CIBMTR):** A research collaboration between the National Marrow Donor Program (NMDP)/Be The match and the Medical College of Wisconsin.

5. **Common Rule:** A Federal Policy for the Protection of Human Subjects codified in separate regulations by the Department of Health and Human Service (DHHS) and other Federal departments and agencies.

5.1. **2018 Revised Common Rule Requirements:** Revised Federal Policy for the Protection of Human Subjects (Revised Common Rule) requirements effective on January 21, 2019.
5.2. **Pre-2018 Common Rule Requirements:** Federal Policy for the Protection of Human Subjects (Common Rule) requirements originally published on June 18, 1991 and effective until January 21, 2019.

6. **IRB of record:** The IRB responsible for conducting the IRB reviews of a study on behalf of a participating study site.

7. **PBSC protocol:** NMDP study titled, *Filgrastim-Mobilized Peripheral Blood Stem Cells for Allogeneic Transplantation with Unrelated Donors*

8. **Research protocol:** General term used to refer to a study proposal, research project, concept paper, etc.

9. **Transplant center initiated research protocol:** A research protocol initiated by the recipient's transplant center where both the recipient and the unrelated donor are considered research subjects. For such research, the NMDP IRB is responsible for the review of protocol procedures that relate only to NMDP unrelated donors; the IRB used by the Principal Investigator's institution is responsible for review of protocol procedures that relate to any study subjects other than NMDP unrelated donors.

10. **Unanticipated problem involving risks to participants or others (UP):** An incident, experience, or outcome that meets all of the following criteria:
    1. ***Unexpected*** (in terms of nature, severity, or frequency) given
        a. The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
        b. The characteristics of the subject population being studied;
    2. ***Related or possibly related to participation in the research*** (i.e., There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.); and
    3. Suggests that the ***research places participants or others at a greater risk of harm*** (including physical, psychological, economic, or social harm) ***than was previously known or recognized***.

RESPONSIBILITIES

1. **NMDP Institutional Official**

- Review, approve, and sign off on reports of determinations of UPs to be sent to OHRP and other applicable agencies.

2. **NMDP IRB Staff**

- Conduct primary review and investigation of potential UPs reported to the NMDP IRB Office.
- Prepare final reports of determinations of UPs.

PROCEDURE

1. **Obligation to report unanticipated problems involving risks to participants or others (UPs)**

1.1. Principal Investigators (PI) at study sites where the NMDP IRB is designated as the IRB of record for the study are required to promptly report potential UPs that occur at their site to the NMDP IRB via the NMDP IRB Reportable Event Form.

1.2. Principal Investigators of transplant center initiated research protocols are required to promptly report potential UPs that occur at their transplant center and that impact NMDP unrelated donors to the NMDP IRB via the NMDP IRB Reportable Event Form. The submission should include the report that was submitted to the transplant center's local IRB.

1.3. Any other individual (e.g., research staff, subject, IRB member, or the general public) may report an incident, experience, or outcome for a research protocol that they are concerned represents a potential UP.

1.4. Incidents that may potentially be considered UPs may also become apparent during continuing renewals; incidents of noncompliance; review of data and safety monitoring reports; protocol violations; deviations; complaints or concerns from subjects or family members; concerns raised by research staff or investigators; or participant injuries, deaths, and hospitalizations.

1.5. UPs should be reported regardless of whether they occur during the study, after study completion, or after participant withdrawal or completion of study related activities.

1.6. UPs should be reported to the IRB as soon as possible, but not later than 10 working days after the investigator becomes aware of the event or problem.

1.7. Events/problems that the investigator believes might meet the definition of a UP must be reported to the NMDP IRB. These include, but are not limited to, the following:

1.7.1. Adverse events that meet the criteria of a UP and occur at a site where the NMDP IRB is designated as the IRB of record for the study.

1.7.2. Adverse events that occur in the context of a transplant center initiated research protocol and that have been determined by the transplant center's IRB to meet the definition of a UP.

1.7.3. Protocol deviations or violations that meet the criteria of a UP and occur at a site where the NMDP IRB is designated as the IRB of record for the study.

1.7.4. Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm.

1.7.5. Other unanticipated events, incidents, or problems that are related to the research and that indicate participants or others might be at new or increased risks, such as:

1.7.5.1. Any event that requires prompt reporting according to the research protocol or the sponsor.
1.7.5.2. Any accidental or unintentional change to the IRB-approved research protocol that involved risks or has the potential to recur.
1.7.5.3. Any change to the research protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
1.7.5.4. Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
1.7.5.5. Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff.
1.7.5.6. Any other event appropriate to the local context.

1.8. When reporting a UP to the IRB, the following information should be submitted in the report:

1.8.1. Study title and NMDP IRB study number (if known)
1.8.2. Detailed description of the UP
1.8.3. Description of corrective actions that have been taken or are proposed in response to the possible UP

2. **Avenues for reporting UPs**

2.1. Reports made by a PI or research staff must be submitted to the NMDP IRB using the NMDP IRB Reportable Event Form.

2.2. Should a person who is not a PI or research staff need to submit a report, the report may be submitted to NMDP IRB staff by alternate means (e.g., email). All reports will be handled promptly and in a confidential manner.

2.2.1. When complaints are received from persons outside the study team, NMDP IRB staff will identify the study associated with the complaint, gather sufficient information, and report it to the PI.

2.2.2. The PI is responsible for promptly addressing and resolving complaints from study participants. When a complaint is made, the PI must assess the incident and determine whether it could be considered an unanticipated problem involving risks to participants or others or potential serious or continuing non-compliance and follow the NMDP IRB reporting requirements. All complaints from study participants must be submitted to the NMDP IRB at the time of the study's continuing review.

2.2.3. The PI must report to the NMDP IRB how the complaint was resolved.

2.2.4. If the complaint is about the PI, the NMDP IRB staff will work with the study team and/or the PI's institution to resolve the complaint.

3. **Preliminary review and investigation of UPs**

3.1. Before the NMDP IRB staff begins their review of a reported UP, they must first determine whether the incident should be investigated, managed, and

resolved by the NMDP IRB staff or by the PI's institutional IRB, if different from the NMDP IRB.

3.1.1. Reports of UPs are to be reviewed by the NMDP IRB staff if:

3.1.1.1. the potential UP occurred at a site that designates the NMDP IRB as their IRB of record for the study; or

3.1.1.2. the UP arises in the context of a transplant center initiated research protocol, and the UP involves NMDP unrelated donors under the jurisdiction of the NMDP IRB; or

3.1.1.3. the research is sponsored by the NMDP, CIBMTR, or BMT CTN, and the report is of an aggregate of events, the frequency of which was considered unexpected by the study's monitoring entity.

3.1.2. Reports of UPs are to be forwarded to the PI's own IRB if the research involves a transplant center initiated research protocol and research subjects other than NMDP unrelated donors.

3.1.2.1. The NMDP IRB staff need not take further action regarding such reports of UPs.

3.1.2.2. If the UP is determined by the PI's own IRB to be a reportable event/problem, the PI will inform the NMDP IRB staff of the confirmed UP, which will then be reported at the next regularly scheduled NMDP IRB meeting. No further action need be taken by the NMDP IRB. However, any further action specific to the participation of NMDP unrelated donors on the protocol shall be made at the discretion of the NMDP IRB.

3.2. If it is determined that the incident should be reviewed by the NMDP IRB staff, pursuant to 3.1.1, NMDP IRB staff, when necessary in coordination with the IRB Chair or an IRB member with relevant subject matter expertise, will: (1) review the UP report, (2) obtain additional information if needed, and (3) make a determination of whether the incident meets the criteria of a UP.

3.2.1. Prior to making the determination, NMDP IRB staff will obtain additional information or input from the following, when applicable:

3.2.1.1. The Medical Monitor for an NMDP/Be The Match or CIBMTR study.

3.2.1.2. The Medical Monitor or Data & Safety Monitoring Board (DSMB) for a **BMT CTN** study.

3.2.1.3. The NMDP Chief Medical Officer for the **PBSC** protocol or **10-CBA** protocol.

3.2.1.4. Should the lack of a response interfere with the IRB's timely decision making for the incident, NMDP IRB staff may choose to forward the report to the convened NMDP IRB at their next regularly scheduled meeting without obtaining input from the above.

3.3. If it is determined that the incident does not meet the criteria of a UP, the report will be closed, documented, and filed.

3.4. If it is determined that the incident does meet the criteria of a UP, the report will be forwarded to the convened NMDP IRB at their next regularly scheduled meeting.

3.4.1. If subjects are at immediate risk of harm, and there is insufficient time to wait for review by the convened IRB, IRB staff will forward the UP report to the IRB Chair, who may immediately halt further enrollment and/or suspend activities for currently enrolled subjects. At the same time, the IRB staff will assign the item to the full board agenda.

3.4.2. The NMDP IRB may choose to meet via conference call or another method at a time other than the regularly scheduled meeting, if necessary, in order to ensure prompt review and/or reporting of the UP.

4. Final review by the convened IRB

4.1. Following receipt of a UP report pursuant to Section 3.4, the convened IRB will complete a final review and determination.

4.2. Copies of the following documents will be forwarded to all members of the IRB for review:

4.2.1. All documentation regarding the UP, such as the original report, information obtained during an investigation, and the intended corrective action plan.

4.2.2. Current NMDP IRB approval letter

4.2.3. Last IRB application

4.2.4. Current approved protocol

4.2.5. Current NMDP IRB-approved consent forms

4.2.6. Any other pertinent information (e.g., Investigator's Brochure, questionnaires, Data Safety Monitoring Board reports, etc.)

4.3. The convened IRB will review the information and make the final determination as to whether the incident meets the criteria of a UP.

4.4. If the IRB determines that the incident does not meet the criteria of a UP, the report will be closed, documented, and filed.

4.5. If the IRB determines that the incident meets the criteria of a UP, they will decide what action(s) to take, which may include one or more of the following:

4.5.1. Modification of the research protocol

4.5.2. Modification of the information disclosed during the consent process

4.5.3. Provision of additional information to past participants

4.5.4. Notification of current participants (required when such information may relate to participants' willingness to continue to take part in the research)

4.5.5. Requirement that current participants re-consent to participation

4.5.6. Modification of the continuing review schedule

4.5.7. Monitoring of the research or consent process

4.5.8. Requirement of additional training or oversight

4.5.9. Closing the research to further enrollment of subjects

4.5.10. Suspension or termination of the research

4.5.11. Referral to other organizational entities (e.g., legal counsel. risk management, Institutional Official)

4.5.12. Other actions as appropriate

5. **Reporting of UPs**

5.1. The Department of Health and Human Services (HHS) and FDA regulations require prompt reporting of unanticipated problems involving risks to participants or others in nonexempt human subjects research.

5.2. Reports of UPs will be prepared by the NMDP IRB staff and shall include the following:

5.2.1. Name of the institution conducting the research

5.2.2. Title of the research protocol and/or grant proposal in which the UP occurred

5.2.3. Name of the PI on the research protocol

5.2.4. NMDP IRB study number and the number of any applicable federal award(s)

5.2.5. Detailed description of the UP

5.2.6. Findings of the NMDP or the NMDP IRB

5.2.7. Actions the NMDP is taking or plans to take to address the UP

5.2.8. Reasons for the NMDP's or the NMDP IRB's actions

5.2.9. Plans for continued investigation or action, if applicable.

5.3. The draft report will be reviewed by the NMDP Institutional Official.

5.4. If the UP occurred at a relying institution, the draft report will be forwarded to the site for review and comment.

5.4.1. The NMDP will make reasonable efforts to allow for the site's review/comment, but in no case will such opportunity interfere with timely submission of required reports.

5.4.2. Although NMDP will consider any comments submitted, the final content of the report is up to the discretion of the NMDP.

5.5. The final report will be reviewed and signed by the NMDP Institutional Official.

5.6. Once the NMDP Institutional Official has signed off on the report, it will be distributed to:

5.6.1. NMDP Organizational Official

5.6.2. Principal Investigator

5.6.3. OHRP

5.6.3.1. For research subject to pre-2018 Common Rule Requirements, reporting to OHRP is not required if, 1) the research is not federally funded, and 2) the relying institution did not "check the box" on its FWA

(i.e., The relying institution did not elect on their FWA to apply the Common Rule and all of its subparts to all of its human subjects research regardless of the source of support.).

5.6.3.2. For research subject to 2018 Revised Common Rule Requirements, reporting to OHRP will only occur for federally-funded studies.

5.6.4. FDA, when the research is subject to FDA regulations

5.6.5. Department of Defense-Navy Human Research Protection Officer, when the research is subject to Department of Defense (DoD) regulations. NOTE: Reporting to DoD must occur within five days of completion of the report.

5.6.6. Other government agencies when the research is overseen or funded by those agencies, and they require reporting separate from that to OHRP

5.6.7. Non-federal study sponsor or contract research organization, when appropriate

5.6.8. BMT CTN Data & Coordinating Center, for BMT CTN studies

5.6.9. Other sites involved in the research, when appropriate

5.6.10. NMDP legal counsel, when appropriate

5.7. The above reports will not be sent to federal regulatory agencies if the agency has already been made aware of the UP through other mechanisms that may have primary reporting responsibilities, such as reporting by the PI, sponsor, or another organization.

5.8. Required reporting will be completed within 30 days of the determination that the incident meets the criteria of a UP. In rare instances, this deadline may be extended for good cause in the discretion of the Institutional Official in consultation with the Organizational Official, in which case a preliminary report would be submitted to the above people/agencies with a follow-up report submitted at a later date when more information is available.

6. Reporting to AAHRPP (Association for the Accreditation of Human Research Protection Programs)

6.1. NMDP will report to AAHRPP as soon as possible but within 48 hours after NMDP or any researcher (if researcher is notified rather than NMDP) becomes aware of:

6.1.1. Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections

6.1.2. Any litigation, arbitration, or settlements initiated related to human research protections

6.1.3. Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the NMDP's human research protection program.

REFERENCES

1. 45 CFR 46.103(b)(5)(i) and 45 CFR 46.116(b)(5)
2. 21 CFR 50.25(b)(5) and 21 CFR 56.108(b)(1)
3. Department of Defense Instruction (DoDI)3216.02, 4.b.4
4. OHRP Guidance on Reporting Incidents to OHRP
5. OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
6. Secretary of the Navy Instruction (SECNAVINST) 3900.39D, para. 8d(2), 8e(6), and 8g(6)

Revision History

Revision	Brief Description of Revision
S00407 rev. 1	New SOP
S00407 rev. 2	Revised section 5.6 re: timing of reports.
S00407 rev. 3	Added Reportable Event Form to Materials. Added definitions of 10-CBA protocol, BMT CTN, IRB of record, and PBSC protocol. Deleted definitions of Internal adverse events and External adverse events. Revised definition of CIBMTR. Added Responsibilities section. Revised 1.1 and 1.7.1. Added 1.7.2, 1.7.3, 2.3, 3.1.1.1, 3.1.1.3, subsections under 3.2, 3.4.1 – 3.4.6, and 5.2.
S00407 rev 4	Made revisions to reflect that the IRB (not the monitoring entity) will make the final determination of whether an event qualifies as a UP. Made revisions to reflect that the IRB (not the BMT CTN DCC) will submit reports to OHRP for BMT CTN studies. These revisions included the following sections: Revised 3.1.1.3 and 3.2. Completely changed 3.2.1 and its subparts. Deleted 3.2.2 and 3.2.3. Deleted previous 3.4.1 – 3.4.6. Deleted previous 5.2 and 5.2.1. Added 5.4.8.
S00407 rev 5	Added 5.1.1. Added 5.3 and 5.4 (that site would have a chance to review the draft report).
S00407 rev 6	Added Common Rule definition and sections 5.6.3.1 and 5.6.3.2 with OHRP reporting requirements.
S00407 rev 7	Clarified section 2 regarding how events should be reported.
S00407 rev 8	Added section 6 on reporting to AAHRPP
S00407 rev 9	Added sections 2.2.1- 2.2.4 regarding complaints. Added note regarding reporting to DoD in 5.6.5.

ADDENDA

Not applicable