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STANDARD OPERATING PROCEDURE

OBJECTIVE/SCOPE

To establish procedures for reporting, investigating, and managing of non-compliance with the National Marrow Donor Program's (NMDP) Human Research Protection Program requirements, and to ensure the prompt reporting of any serious or continuing non-compliance as required by federal regulations.

MATERIALS

Reportable Event Form

SAFETY

Not applicable

DEFINITIONS

1. **Allegation of non-compliance:** A report of an incident of actual or suspected non-compliance that has not yet been established by evidence or investigation.

2. **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

3. **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.

4. **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.
   - 4.1. **2018 Revised Common Rule Requirements:** Revised Federal Policy for the Protection of Human Subjects (Revised Common Rule) requirements effective on January 21, 2019.
   - 4.2. **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.

5. **Continuing non-compliance:** A series or pattern of more than one incident of non-compliance that indicates a deficiency in knowledge, ability, or willingness to comply with a law, regulation, or policy governing human subjects research.

6. **Federalwide Assurance (FWA):** A document filed with the Department of Health and Human Services (HHS) stating that the institution will comply with HHS protection of human subjects regulations.

7. **Finding of non-compliance:** A report of an incident of actual or suspected non-compliance that is confirmed by a preponderance of the evidence or is determined to be true through investigation.

8. **IRBManager:** Web-based system for IRB application submission, IRB application review, and management of IRB-related study records.

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

10. **NMDP IRB staff:** Includes the job positions of IRB Administrator and Program Managers.

11. **Non-compliance:** Failure to comply with laws or regulations governing human subjects research, NMDP human subject research policies or procedures, or the requirements or determinations of the NMDP IRB. Protocol deviations that do not affect the rights and welfare of human subjects are not considered non-compliance.

12. **Principal Investigator (PI):** The individual responsible for the design, conduct, and reporting of research involving human subjects.

13. **Protocol deviation:** A departure from IRB-approved protocol procedures that is unintentional and discovered after it occurs. The protocol deviation is not a result of willful or knowing misconduct by the investigator or research staff.

14. **Relying institution:** A participating study site that enters into a reliance agreement to rely on another IRB, rather than their own local IRB, for review and continuing oversight of the study at their institution.

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

16. **Serious non-compliance:** Non-compliance that violates the rights and welfare of research subjects, increases risks to subjects, or compromises the integrity of data.

17. **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.

RESPONSIBILITIES

1. NMDP Institutional Official

- Review, approve, and sign off on reports of determinations of serious or continuing non-compliance to be sent to the Office for Human Research Protections (OHRP) and other applicable agencies.

2. **NMDP IRB Administrator**

- Conduct secondary review of reports of allegations of non-compliance

3. **NMDP IRB Staff**

- Conduct primary review and investigation of allegations of non-compliance
- Prepare reports of determinations of serious or continuing non-compliance to be sent to OHRP and other applicable agencies
- Distribute reports of determinations of serious or continuing non-compliance

4. **Principal Investigator**

- Report potential serious or continuing non-compliance to the NMDP IRB using the Reportable Event Form

PROCEDURE

1. Obligation to Report Non-compliance

1.1. All members of the NMDP community involved in human subjects research—including, but not limited to, PIs, collaborating researchers, research staff, auditors, CIBMTR staff, and NMDP/Be The Match staff—are expected to comply with the highest standards of ethical and professional conduct, with federal law and regulations, and applicable NMDP IRB policies and procedures. As such, they are responsible for promptly reporting all suspected or actual incidents of non-compliance.

1.2. Allegations of non-compliance should include, if known, the title of the research, names of the persons involved in the non-compliance, a detailed description of the non-compliance, and any evidence or documentation to support the alleged non-compliance.

1.3. PIs, specifically, are required to submit reports of non-compliance on their protocols, non-compliance found as a result of a monitoring visit or audit, and any other incident of non-compliance reported to or observed by them.

1.4. Research participants and participants' family members are also encouraged to report suspected non-compliance. To that end, the NMDP requires research consent forms to include information regarding whom to contact if the research subject has a complaint.

2. Avenues for Reporting Non-compliance

2.1. PIs and research staff must use the Reportable Event Form in IRBManager when reporting non-compliance to the NMDP IRB.

2.1.1. Potential serious and/or continuing non-compliance 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.

2.2. If persons other than the PI or research staff wish to report non-compliance to the NMDP IRB, they may do so in person, in writing, or by telephone. The complainant or reporter may choose to remain anonymous. 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. Primary Review and Investigation of Allegations of Non-compliance

3.1. Before the NMDP IRB staff begins their review of allegations of non-compliance, 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. Allegations of non-compliance are to be reviewed by the NMDP IRB staff if:

3.1.1.1. the research is sponsored by the NMDP or CIBMTR, and the non-compliance may have study-wide implications; or

3.1.1.2. the NMDP IRB is the IRB of record for the study at the site where the incident occurred; or

3.1.1.3. the allegation of non-compliance arises in the context of a transplant center initiated research protocol and involves NMDP unrelated donors.

3.1.2. Allegations of non-compliance 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 make any judgment regarding these allegations.

3.1.2.2. If the non-compliance was determined by the PI's IRB to be serious and/or continuing, the PI will inform the NMDP IRB at the time of continuing review. Any 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 investigated, managed, and resolved by the NMDP IRB staff, NMDP IRB staff will: (1) review the information accompanying the allegation of non-compliance, (2) assess what additional information is needed to make a determination regarding the validity of the allegation, and (3) attempt to obtain additional information, if needed, through investigation.

3.2.1. NMDP IRB staff is responsible for obtaining as much information as possible from the individual who reported the event, including but not limited to: the facts present to date, the identification of individuals involved in the incident, and any documentation related to the report.

3.2.2. In addition, NMDP IRB staff may need to review other written materials, interview knowledgeable sources, and collect other documentation.

3.2.3. If the allegation of non-compliance cannot be investigated adequately, it will be referred to the NMDP Institutional Official.

3.3. Based on a review of the above information, NMDP IRB staff will make one of the following determinations:

3.3.1. The allegation of non-compliance is not substantiated or confirmed and, therefore, no further review or action is needed.

3.3.1.1. These reports will be closed, documented, and filed.

3.3.2. The allegation of non-compliance is substantiated by a preponderance of evidence and is therefore a finding of non-compliance.

3.3.2.1. A finding of non-compliance requires no further review if the non-compliance is neither serious nor continuing. In that case, it may be addressed through a corrective action plan to remedy the problem.

3.3.2.1.1. If a corrective action plan was not received with the original report of non-compliance, NMDP IRB staff will request a plan from the PI.

3.3.2.2. If, however, in the judgment of the NMDP IRB staff, the non-compliance meets the definition of serious and/or continuing non-compliance, the report will be forwarded to the IRB Administrator for a secondary review.

3.3.2.3. NMDP IRB staff may also forward the report to the IRB Administrator if they question whether or not an incident of non-compliance should be considered serious and/or continuing or they question whether or not the intended corrective action plan is adequate.

3.4. Where an allegation of non-compliance is resolved administratively under 3.3.1 or 3.3.2.1 of this Section, the NMDP IRB office will provide written

correspondence to the complainant and the PI with its determination regarding the non-compliance and justification for actions taken.

3.5. The NMDP IRB will receive a report of all allegations of non-compliance resolved administratively under 3.3.1 or 3.3.2.1 of this Section at its next regularly scheduled meeting.

4. Secondary Review: Confirming Whether Non-compliance is Serious and/or Continuing

4.1. Following receipt of a report of non-compliance pursuant to Section 3.3.2.2, the IRB Administrator will use the information gathered by NMDP IRB staff during its investigation to determine if: (1) the NMDP IRB staff's finding of non-compliance is, in fact, not non-compliance; (2) the non-compliance is neither serious nor continuing; or (3) the non-compliance is serious and/or continuing.

4.1.1. If the IRB Administrator decides, in contradiction to the NMDP IRB staff, that the incident does not meet the definition of non-compliance, the report will be closed, documented, and filed.

4.1.2. If the IRB Administrator decides that the non-compliance is neither serious nor continuing, the non-compliance will be resolved with corrective action, pursuant to 3.3.2.1, and does not need to be forwarded to the convened IRB.

4.1.3. If the IRB Administrator determines that the non-compliance is serious and/or continuing, the report will be forwarded to the convened IRB for final review and determination.

4.1.4. The IRB Administrator may decide that further information is needed to make a determination. In such cases the NMDP IRB staff will attempt to obtain the necessary additional information.

5. Final Review and Determination by the Convened IRB

5.1. Following receipt of a report of non-compliance pursuant to Section 4.1.3, the convened IRB will complete a final review and determination of non-compliance.

5.2. The IRB will review all documentation regarding the non-compliance, such as the original report (e.g., Reportable Event Form), information obtained during an investigation, the PI's intended corrective action plan, and recommendations of the IRB Administrator.

5.3. The IRB will have access to other study information and documents via IRBManager.

5.4. At a convened IRB meeting, the IRB will make one of the following determinations:

5.4.1. Additional information is needed for the IRB to make their determinations.

5.4.1.1. The IRB may request that such information be obtained before further action is taken.

5.4.2. The non-compliance is not substantiated, and no further action is required;

5.4.3. The non-compliance occurred but is neither serious nor continuing and recommends a corrective action plan; or

5.4.4. The non-compliance is serious and/or continuing.

5.4.4.1. The IRB will then determine corrective action as detailed in Section 5.5 and report the non-compliance as required in Section 6.

5.5. If the convened IRB agrees that the non-compliance is serious and/or continuing, they will decide what action(s) to take, which may include one or more of the following:

5.5.1. Modification of the research protocol

5.5.2. Modification of the information disclosed during the consent process

5.5.3. Provision of additional information to past participants

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

5.5.5. Requirement that current participants re-consent to participation

5.5.6. Modification of the continuing review schedule

5.5.7. Monitoring of the research or consent process

5.5.8. Requirement of additional training or oversight

5.5.9. Closing the research to further enrollment of subjects

5.5.10. Suspension or termination of the research

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

5.5.12. Other actions as appropriate

5.6. 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 non-compliance.

6. Reporting of Serious or Continuing Non-compliance

6.1. The Department of Health and Human Services (HHS) and the U.S. Food and Drug Administration (FDA) regulations require prompt reporting of serious or continuing non-compliance in nonexempt human subjects research.

6.2. Reports of serious and/or continuing non-compliance will be prepared by the NMDP IRB staff and shall include the following:

6.2.1. Name of the institution conducting the research

6.2.2. Title of the research protocol and/or grant proposal in which the non-compliance occurred, or, for IRB or institutional noncompliance, the IRB or institution involved

6.2.3. Name of the PI on the research protocol

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

6.2.5. Detailed description of the non-compliance

6.2.6. Findings of the NMDP or the NMDP IRB

6.2.7. Actions the NMDP is taking or plans to take to address the non-compliance

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

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

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

6.4. If the non-compliance occurred at a relying institution, the draft report will be forwarded to the site for review and comment.

6.4.1. 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.

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

6.5. The final report will be approved and signed by the NMDP Institutional Official.

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

6.6.1. NMDP Organizational Official

6.6.2. Principal Investigator

6.6.3. Office of Human Research Protections (OHRP)

6.6.3.1. 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.).

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

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

6.6.5. Department of Defense-Navy Human Research Protection Officer, when the research is subject to Department of Defense regulations.

NOTE: Reporting to DoD must occur within five business days of completion of the report.

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

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

6.6.8. BMT CTN Data & Coordinating Center (DCC), for BMT CTN studies

6.6.9. Other sites involved in the research, when appropriate

6.6.10. NMDP legal counsel, when appropriate

6.7. Required reporting will be completed within 30 days of the determination that the non-compliance is serious and/or continuing. In rare instances, this deadline may be extended for good cause at 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.

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

7.1. 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:

7.1.1. 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

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

7.1.3. 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)(2)
3. Department of Defense Instruction (DoDI)3216.02, 3.1(h)(1)
4. OHRP Guidance on Reporting Incidents to OHRP
5. Secretary of the Navy Instruction (SECNAVINST) 3900.39E

Revision History

Revision	Brief Description of Revision
S00213 version 1.0	New SOP
S000213 version 1.1.	Formatting changes.
S00213 rev. 2	Put SOP into new format. Added applicable reference documents. Added definition for "allegation of non-compliance." Changed "suspected non-compliance" to "allegations of non-compliance" throughout document. Added Sections 6.3.4 and 6.3.5. Added Sections 7.4.5 and 7.4.8.
S00213 rev. 3	Added several definitions and made major revisions to entire Procedure.
S00213 rev. 4	Simplified 2.1. Clarified 6.4.5. Added DoDI reference doc.
S00213 rev. 5	Revised section 6.6 re: timing of reports.
S00213 rev. 6	Added Reportable Event Form under Materials. Added definitions for BMT CTN, IRB of record, and Relying institution. Revised definition of CIBMTR. Added Responsibilities section. Added sections 2.3, 3.1.1.2, 6.1.1, 6.3, 6.4, and 6.6.8.
S00213 rev. 7	Added Common Rule definition. Added 6.6.3.1 and 6.6.3.2 with OHRP reporting requirements.
S00213 rev. 8	Added definition of IRBManager. Revised sect 2 to reflect reporting via IRBManager. Revised sect 3.1.2.2 to clarify notification of IRB at time of continuing review. Revised sect 5.3 to reflect IRBManager.
S00213 rev. 9	Clarified 3.1.1.1.
S00213 rev. 10	Added section 7 on reporting to AAHRPP
S00213 rev. 11	Added sections 2.2.1 – 2.2.4 regarding complaints.
S00213 rev. 12	Changed title from Sr. Human Research Protection Program Specialist to Program Managers. Added 2.1.1 regarding timeframe for reporting. Added a note to 6.6.5 re: reporting to DoD. Removed 6.7 re: not copying federal agencies on reports that had already been reported by another entity. Removed DoDD 3216.2 from References.

ADDENDA

Not applicable