STANDARD OPERATING PROCEDURE

OBJECTIVE/SCOPE

To ensure that the National Marrow Donor Program (NMDP) Institutional Review Board (IRB) uses a standard set of criteria to determine a Principal Investigator's qualifications to perform research, and a standard set of criteria to review the proposed research.

MATERIALS

Not applicable

SAFETY

Not applicable

DEFINITIONS

1. **Blood and Marrow Transplant Clinical Trials Network (BMT CTN):** Conducts large multi-institutional clinical trials addressing important issues in hematopoietic cell transplantation thereby furthering understanding of the best possible treatment approaches.

2. **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.

3. **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.
   - 3.1. **2018 Revised Common Rule Requirements:** Revised Federal Policy for the Protection of Human Subjects (Revised Common Rule) requirements effective on January 21, 2019.
   - 3.2. **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.

4. **Consultant:** An individual who has been invited to assist in the review of research which requires expertise beyond or in addition to that of the NMDP IRB members.

5. **IRB Authorization Agreement:** An agreement between two institutions that defines the scope of research that one institution's qualified IRB will be allowed to review on behalf of the other institution. Also referred to as a reliance agreement.

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

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

8. **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.

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

10. **Senior Management:** Officers at the NMDP including, but not limited to, the positions of Chief Executive Officer, Chief Medical Officer, Chief Financial Officer, Chief Information Officer, and Chief Legal & Policy Officer.

11. **Single IRB (sIRB):** One IRB that has been selected to serve as the IRB of record for the participating sites on a multi-site study.

12. **Vulnerable subjects:** Human research subjects who are likely to be vulnerable to coercion or undue influence.

RESPONSIBILITIES

1. **NMDP IRB Staff**

- Conduct pre-reviews of all research studies submitted to the NMDP IRB for initial review, continuing review, study amendments, and study closure
- Create the agenda for convened IRB meetings
- Distribute meeting materials to IRB members
- Assign primary and secondary reviewers for study submissions being reviewed at convened IRB meetings
- Secure external consultants as necessary
- Report in writing findings and actions of the NMDP IRB to the Principal Investigator (PI) and the Principal Investigator's institution

2. **IRB Chair, or designee**

- Approve in advance any guests attending the convened IRB meeting

PROCEDURE

1. **Administrative review to determine type of IRB review**

1.1. IRB staff shall conduct an administrative review of initial submissions to determine the type of initial review (i.e., full review, expedited review, or determination of exempt status). (Refer to S00041 *NMDP IRB Expedited, Emergency, and Exempt from Regulation*). The IRB Administrator may be consulted for such determination if needed.

2. Pre-review by NMDP IRB staff prior to review by NMDP IRB

2.1. NMDP IRB staff will conduct a pre-review of all research studies submitted to the NMDP IRB for initial review, continuing review, study amendments, and study closure. All materials submitted will be reviewed for completeness. The elements outlined in the S00038 *NMDP IRB Materials Required for Review* will be used as the basis for the pre-review. NMDP IRB staff will contact the Principal Investigator if there is additional information or materials that must be obtained prior to NMDP IRB review of the study.

2.2. During the pre-review, NMDP IRB staff will review the list of investigators banned by the FDA from performing research to ensure that the study's Principal Investigator is not included on the list. Investigators currently banned by the FDA will not be allowed to conduct research through the NMDP.

3. Meeting agenda

3.1. IRB staff shall create the agenda for convened IRB meetings.

3.2. Initial review of research that requires review by the convened IRB shall be conducted at the next regularly scheduled IRB meeting, provided there is sufficient time on the agenda, and provided the IRB Office receives the study materials by the submission deadline for that meeting.

3.3. Continuing review of research that requires review by the convened IRB shall be scheduled appropriately so as to avoid a lapse in IRB approval.

3.4. There is no limit placed on the number of items on the meeting agenda. However, adequate time for discussion of all items on the agenda will be considered when creating the agenda.

3.5. In the event that there is not enough time to adequately discuss all items on the agenda, at the discretion of the IRB Chair and IRB staff, some items may be tabled until the next convened meeting of the IRB.

4. Distribution of meeting materials

4.1. For all types of reviews, primary and secondary reviewers shall have access to complete documentation for the studies to be reviewed. These materials will include, but are not limited to, the materials outlined in SOP S00038 *NMDP IRB Materials Required for Review*. All NMDP IRB members will have access to the complete study documentation via IRBManager.

4.2. Meeting materials will be available in IRBManager one week prior to the scheduled meeting. If necessary, IRB staff may distribute materials by another method such as an express delivery service, courier, postal mail, fax, or electronically.

5. Primary/secondary review method

5.1. The NMDP IRB employs the use of primary and secondary reviewers. The primary and secondary reviewers receive complete study documentation for review, summarize the study documentation for the other NMDP IRB members, and lead the discussion.

5.1.1. The primary/secondary review method may be used for any type of review, including, but not limited to, initial review, continuing review, review of study amendments, review of reports of unanticipated problems involving risks to subjects or others, and review of serious or continuing non-compliance.

5.1.2. Assignments of primary and secondary reviewers are made by IRB staff according to the type of research (i.e., biomedical or social/behavioral) and the scientific or scholarly expertise of the reviewer.

5.2. If an IRB member has a financial or other conflict of interest pertinent to a research protocol to which he/she has been assigned as a primary or secondary reviewer, he/she shall promptly notify the NMDP IRB staff, so that the study may be reassigned to another primary or secondary reviewer.

5.3. If the primary reviewer feels he/she does not have the expertise required to review the protocol, he/she shall promptly notify the NMDP IRB staff, and the study will be reassigned to another primary reviewer.

5.3.1. If the appropriate expertise is not available among the IRB members, the IRB may defer to another meeting, or IRB staff will secure an external consultant reviewer.

5.3.1.1. The consultant will be required to disclose any possible conflict of interest with the protocol, investigator, or any member of the investigator's team.

5.3.1.2. Once it is confirmed that the consultant has no actual or perceived conflicts of interest, the consultant will be provided with the same study information that the primary reviewer receives, along with the IRB's and/or primary reviewer's questions.

5.3.1.3. The consultant must provide his/her review comments in writing to the IRB. This information shall be provided to the IRB members at the meeting or sent to the members prior to the meeting.

5.3.1.3.1. If deemed necessary by the IRB members or the IRB Chair, the consultant may be invited to attend the IRB meeting to discuss the protocol.

6. Focus of NMDP IRB review

6.1. In a research study conducted by a transplant center investigator where both a hematopoietic cell transplant recipient and a donor are research subjects, the research study will usually be reviewed by both the IRB at the transplant center where the recipient will be treated and by the NMDP IRB. In these

cases the review by the NMDP IRB will focus on issues related to unrelated donor participation (e.g., donor safety, donor risks, donor benefits, and donor informed consent). However, when reviewing the study for donor participation, the NMDP IRB will take into consideration the risk-benefit ratio for recipients in regard to its effect on the rights and welfare of donors.

6.1.1. The NMDP IRB may make recommendations to the transplant center IRB about recipient related study factors, should they choose to do so.

6.2. NMDP IRB review of CIBMTR research studies will focus on both recipient and donor safety, risks, benefits and informed consent.

6.3. For multi-site studies where the NMDP IRB is serving as the IRB of record for participating study sites, the NMDP IRB will review the study for the protection of all research subjects.

7. **Processes used to supplement the IRB's initial review, continuing review, review of study amendments, review of unanticipated problems involving risks to subjects or others, or review of serious and/or continuing non-compliance.**

7.1. Subcommittees composed of IRB members and/or consultants may be formed at the request of the Chair to address 1) process issues (e.g., minor assent, etc.), 2) knowledge issues (e.g., genetic engineering, etc.), 3) unanticipated problem issues or 4) non-compliance issues.

7.1.1. Subcommittees will report findings back to the convened IRB for consideration in IRB deliberations.

7.1.2. Subcommittee findings will be documented in the IRB study file and/or meeting minutes.

7.2. The primary reviewer, or IRB Chair, may determine that Principal Investigators or other consultants should be invited to an IRB meeting to provide additional information regarding 1) a specific protocol, 2) a specific unanticipated problem or 3) a specific non-compliance issue.

7.2.1. The IRB Chair, or designee, must approve in advance of the meeting any guests attending the meeting.

7.2.2. After approval has been obtained, consultants may be invited directly by the primary reviewer or IRB Chair, or IRB members may refer the IRB staff to individuals to contact for consultation.

7.2.3. Potential consultants will be asked to disclose any possible conflict of interest with the protocol, investigator, or any member of the investigator's team.

7.2.3.1. If the consultant has a conflict of interest, efforts will be made by the NMDP IRB to find a different consultant.

7.2.3.2. If another consultant cannot be found or is not available, the IRB may still invite the consultant with the conflict of interest to provide additional information to the IRB.

7.2.4. Consultants may not participate in the deliberations or vote of a project. Also, consultants may only attend the portion of the meeting for which they were invited to provide input.

7.2.4.1. If unable to attend the meeting, consultants may also provide the requested additional information to the IRB in writing. This information shall be provided to the IRB members at the meeting or sent to the members prior to the meeting.

7.2.5. Principal Investigators who have attended an IRB meeting to provide additional information must absent themselves from the meeting room during deliberation and voting.

7.2.6. Documentation of discussion with invited guests will be included in the meeting minutes.

7.2.7. Documentation provided in writing by consultants will be maintained in the IRB study file.

8. Initial review

8.1. Each proposed research study will be reviewed in three broad categories:

8.1.1. Qualifications of the Principal Investigator.

8.1.2. The application/research protocol.

Note: The research protocol will be reviewed by the "Criteria for IRB Approval of Research" outlined in 45 CFR 46.

8.1.3. The informed consent process and document(s).

9. Qualifications of the Principal Investigator

9.1. All Principal Investigators must provide documentation to the NMDP IRB that will allow the NMDP IRB to determine if the Principal Investigator is qualified to perform the proposed research.

9.2. The requested documentation pertaining to the Principal Investigator may include but is not limited to the following:

9.2.1. Curriculum Vitae (CV), which will be reviewed for:

9.2.1.1. Degrees.

9.2.1.2. Credentials to conduct research.

9.2.1.3. Experience in the area of the proposed research.

9.2.2. Training in human subjects' protection.

9.2.2.1. Principal Investigators from institutions outside of the U.S. are required to follow their own institution's and country's regulations regarding human research protection training requirements. Proof of such training may not be available; however, these Principal

Investigators will be asked if they are in compliance with their institution's training requirements and their country's regulations.

9.2.3. Financial disclosure/conflict of interest statement, if applicable.

10. Application/research protocol

10.1. The initial review of the application/research protocol will include, but is not limited to, the following points required by the federal regulations:

10.1.1. Is the proposed research design scientifically sound and will not unnecessarily expose subjects to risk?

10.1.1.1. Is the hypothesis clear?

10.1.1.2. Is the study design appropriate to prove the hypothesis?

10.1.1.3. Will the research contribute to generalizable knowledge, and is it worth exposing the subjects to risk?

10.1.1.4. The NMDP IRB may wish to draw upon additional expertise, such as scientific review committees or consultants, to help answer these questions regarding scientific soundness of the research design.

10.1.2. Are the risks to subjects reasonable in relation to the anticipation of benefits, if any, to the subjects, and to the importance of knowledge that may reasonably be expected to result?

10.1.2.1. What does the NMDP IRB consider the level of risk to be?

10.1.2.2. Is there any benefit to the subject?

10.1.3. Are risks to subjects minimized?

10.1.3.1. Does the research design minimize risk to subjects?

10.1.3.2. Would additional research oversight provide better subject safety?

10.1.4. Is subject selection equitable?

10.1.4.1. Who is to be enrolled?

10.1.4.2. Are these subjects appropriate for the protocol?

10.1.5. Are additional safeguards in place for subjects likely to be vulnerable to coercion or undue influence (i.e., vulnerable subjects such as children, pregnant women, socially or economically disadvantaged persons, etc.)?

10.1.6. Are subject privacy and data confidentiality maximized?

10.1.6.1. How will the privacy of subjects during recruitment, study procedures and follow-up be protected?

10.1.6.2. Will personally identifiable research data be protected to the extent possible from access and use?

10.1.6.3. How will confidentiality of data and/or samples be protected during storage and use?

10.1.6.4. How and when will data be destroyed (if applicable)?

10.1.6.5. Are any special privacy and confidentiality issues properly addressed, (e.g., use of genetic information)?

10.1.6.6. If the study receives funding by the Department of the Navy (DON), has the study been reviewed for scientific merit?

10.1.7. Does the study include any research procedures that are contrary to NMDP Standards (e.g., a research blood collection volume that exceeds the limit set by the Standards)? The NMDP Chief Medical Officer has determined that the NMDP IRB may approve research procedures that are contrary to NMDP Standards.

11. Informed consent

11.1. The initial review of the informed consent process will include, but is not limited to, the following points required by the federal regulations:

11.1.1. Is informed consent obtained from subjects?

11.1.2. Does the informed consent document include the basic elements of informed consent? (45 CFR 46.116)

11.1.3. Is the informed consent document understandable to subjects?

11.1.4. Who will obtain informed consent (e.g., Donor Center Coordinator, PI, etc.)?

11.1.5. May the informed consent requirement be waived or altered (if requested by investigator)?

11.1.6. May the documentation of informed consent be waived (if requested by investigator)?

11.2. If the NMDP IRB is serving as the IRB of record for study sites, and the study involves children as subjects, the assent process will also be reviewed by the IRB, for example:

11.2.1. Will assent be obtained from subjects who are children?

11.2.2. Do the procedures for obtaining and documenting assent meet the federal regulations?

12. Advertisements

12.1. The IRB must review advertisements intended to recruit subjects to the study, taking into account the information contained in the advertisement and the mode of its communication.

12.2. The IRB must review the final copy of printed, audio or video taped advertisements.

12.2.1. If the IRB makes changes to an advertisement, the final copy must be reviewed by the IRB to ensure the changes were made.

12.2.1.1. This includes the final production of an audio or video taped advertisement.

12.2.1.2. Depending on the changes required by the IRB, the final copy may be reviewed administratively.

13. Research involving vulnerable subjects

13.1. In order to approve research where some or all of the subjects are likely to be vulnerable, the IRB will determine whether additional safeguards are in place to protect the rights and welfare of those subjects.

13.1.1. In order to approve research involving **pregnant women, fetuses, or neonates** as subjects, the IRB will determine whether additional safeguards have been included in the protocol as required by Subpart B of the Common Rule, or equivalent protections as allowed by law. This includes an appropriate consent process as required by Subpart B or equivalent laws or regulations.

13.1.1.1. For studies funded by DON, when applying Subpart B, "biomedical knowledge" shall be replaced with "generalizable knowledge."

13.1.1.2. For studies funded by DON, the applicability of Subpart B is limited to research involving:

13.1.1.2.1. Pregnant women as human subjects involved in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus; or

13.1.1.2.2. Fetuses or neonates as human subjects.

13.1.1.3. For studies funded by DON, research involving human subjects using fetal tissue shall comply with US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

13.1.2. The NMDP IRB shall make determinations regarding the approval of research involving **children** as subjects when the NMDP IRB serves as the IRB of record for study sites.

13.1.2.1. In order to approve research involving children as subjects, the IRB will determine whether additional safeguards have been included in the protocol as required by Subpart D of the Common Rule, or equivalent protections as allowed by law. This includes an appropriate assent process for children and consent process for parents or guardians as required by Subpart D or equivalent laws or regulations.

13.1.2.2. The IRB also must consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research. In assessing the risks and potential benefits, the IRB should consider the circumstances of the children to be enrolled in the study (e.g., their health status, age, and ability to understand what is involved in the research) as well as potential benefits to subjects, other children with the same disease or condition, or society as a whole.

13.1.2.3. The primary reviewer will be responsible for providing the IRB with the protocol specific information supporting determinations made in accordance with 45 CFR 46 Subpart D (i.e., §46.404, §46.405, §46.406, or §46.407). This determination will be documented in the IRB meeting minutes.

13.1.2.4. The IRB meeting minutes will document the IRB's determinations regarding requirements for obtaining assent of children and permission

of the parents or guardians, including the process to document assent, if required by the IRB.

13.1.2.5. For studies funded by DON, research involving children as human subjects cannot be exempt.

13.1.3. The NMDP considers NMDP **unrelated donors** to be vulnerable subjects in recipient research protocols where the unrelated donor is also considered a research subject. The NMDP IRB regularly reviews this type of research.

13.1.3.1. As an additional safeguard for the inclusion of NMDP unrelated donors in research, at least one primary member of the NMDP IRB must have experience as a donor advocate. (Refer to S00037 *NMDP IRB Membership and Voting Requirements*)

13.1.3.2. Donor center staff at donor centers that use the NMDP IRB must complete the CITI training course in the protection of human subjects if they are engaged in research where NMDP unrelated donors are considered research subjects. The CITI training includes modules on informed consent and vulnerable subjects.

13.1.3.3. In addition, the NMDP IRB applies the following additional criteria for protections when reviewing a research protocol where NMDP unrelated donors are considered vulnerable subjects:

13.1.3.3.1. The research must not target unrelated donors as a matter of convenience.

13.1.3.3.2. The recruitment process includes additional safeguards to minimize coercion and undue influence.

13.1.3.3.3. The consent process includes additional safeguards to minimize coercion and undue influence.

13.1.3.3.4. The financial payment (if any) to unrelated donors is not coercive or unduly influential.

13.1.3.3.5. The IRB will consider the nature of the risk and the nature and level of anticipated benefit in addition to the availability of alternatives.

13.1.4. Other than research involving unrelated donors, the NMDP IRB does not regularly review research involving other groups of vulnerable populations that do not have specific Common Rule protections (e.g., handicapped, mentally disabled, economically disadvantaged, educationally disadvantaged, or persons with diminished decision-making capacity, etc.). However, should a research protocol that includes such groups of vulnerable subjects be submitted to the NMDP IRB, the IRB would apply the following additional criteria for protections:

13.1.4.1. The research must not target vulnerable subjects as a matter of convenience.

13.1.4.2. The recruitment process includes additional safeguards to minimize coercion and undue influence.

13.1.4.3. The consent process includes additional safeguards to minimize coercion and undue influence.

13.1.4.4. The financial payment (if any) to participants is not coercive or unduly influential.

13.1.4.5. The IRB will consider the nature of the risks, the type of vulnerability and the nature and level of anticipated benefit in addition to the availability of alternatives.

13.1.4.6. The IRB may consider enlisting the expertise of a consultant when reviewing such research.

13.2. NMDP and CIBMTR do not conduct research that intentionally targets the following groups as subjects:

13.2.1. any person captured, detained, held, or otherwise under the control of Department of Defense personnel (e.g., prisoners of war). [Refer to SECNAVINST 3900.39D, para. 6a(8)]

13.2.2. **prisoners**

13.2.2.1. NMDP does not facilitate donation of blood or hematopoietic cell products by prisoners.

13.2.2.2. If an NMDP unrelated donor participating on a research protocol becomes incarcerated, the NMDP IRB office should be promptly notified.

13.2.2.2.1. The NMDP IRB Administrator and/or NMDP IRB Chair will determine if research interaction with the unrelated donor/subject should be ceased during the time of incarceration or if the unrelated donor/subject should be withdrawn from the study.

13.2.2.3. For studies involving transplant recipients as human subjects, and the transplant center is using its own IRB for the study, it is up to the investigator at the individual transplant center to follow his/her own institution's policies and procedures regarding an enrolled subject (who is also a transplant recipient) that becomes incarcerated.

13.2.2.4. For studies involving human subjects other than NMDP unrelated donors, and the participating study site is relying on the NMDP IRB for the study, a subject who becomes incarcerated during the course of the study must be withdrawn from the study. If the Principal Investigator at the study site that has enrolled the subject feels it is in the best interest or safety of the subject to remain enrolled in the study, the study site must have the study reviewed by an IRB that is compliant with the regulations at 45 CFR 46 Subpart C. The NMDP IRB is not constituted to review research involving prisoners.

13.2.3. adults with questionable decision-making capacity

13.2.3.1. If an investigator wishes to recruit to a study an adult who lacks the ability to consent (and who is also a transplant recipient), the investigator must follow his/her own institution's policies and procedures for enrolling such subjects on the study.

13.3. For Department of Defense-supported research:

13.3.1. If consent is to be obtained from the experimental subjects' legal representative, the research must intend to benefit the individual participant.

13.3.2. The determination that research is intended to be beneficial to the individual experimental subject must be made by an IRB.

14. Research involving investigational or unlicensed test articles

14.1. When research involves the use of a drug other than a marketed drug in the course of medical practice, the IRB shall confirm that the drug either has an investigational new drug (IND) application or the research protocol meets one of the FDA exemptions from the requirement to have an IND [21 CFR 312.2(b)]. This is confirmed by the investigator submitting to the IRB the FDA acceptance letter indicating the IND number.

14.1.1. If the investigator states in the IRB application that the research protocol meets one of the FDA exemptions from the requirement to have an IND, and the NMDP IRB questions this determination, the investigator shall be asked for information from his/her IRB justifying the determination of an exemption from IND requirements.

14.2. When research is conducted to determine the safety or effectiveness of a device, the IRB shall confirm that the device has an investigational device exemption (IDE), the device fulfills the requirements for an abbreviated IDE [21 CFR 812.2(b)(1)], or the research protocol meets one of the FDA exemptions from the requirement to have an IDE [21 CFR 812.2(c)]. This is confirmed by the investigator submitting to the IRB the FDA acceptance letter indicating the IDE number.

14.2.1. If the investigator states in the IRB application that the research protocol meets one of the FDA exemptions from the requirement to have an IDE, and the NMDP IRB questions this determination, the investigator shall be asked for information from his/her IRB justifying the determination of an exemption from IDE requirements.

15. Determination of significant vs. non-significant risk in device studies

15.1. In the case of device studies, the NMDP IRB is responsible for confirming a sponsor's determination that a device poses significant (SR) or non-significant risk (NSR).

15.1.1. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final.

15.2. 21 CFR part 812 defines a SR study as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and is:

15.2.1. Intended as an implant; or

15.2.2. Used in sustaining or supporting life; or

15.2.3. Of substantial importance in diagnosing, curing, mitigating or treating disease; or

15.2.4. Otherwise presents a potential for serious risk to the health, safety, or welfare of the subject.

15.3. A NSR study is one that doesn't meet the definition of a significant risk study.

15.4. If the NMDP IRB determines that the study is a SR study, the NMDP IRB must:

15.4.1. Notify the Principal Investigator and the designate Institutional Official of the SR decision. It will be the responsibility of the Principal Investigator to notify the sponsor of the SR decision by the NMDP IRB.

15.4.2. Review the study by the criteria outlined in the "Application/Study Protocol" and "Informed Consent" sections of this SOP once the sponsor has obtained the IDE from the FDA.

15.5. If the NMDP IRB determines that the study is a NSR study, the NMDP IRB will proceed to review the study by the criteria outlined in the "Application/Research Protocol" and "Informed Consent" sections of this SOP.

16. Determination of review interval

16.1. The NMDP IRB will review all research studies in accordance with FDA regulations and the Common Rule, when applicable. At the time of the initial approval, the NMDP IRB will determine the review interval. The basis for the frequency of the review interval may be based on, but is not limited to, risk to the subject for participating in the study, whether the study is eligible for expedited review, and the current status of the study. If the risk to the subject shifts during the course of the study, the NMDP IRB can establish a new review interval.

17. Determination of which studies require verification from sources other than the investigator

17.1. The NMDP IRB shall use the following criteria to determine if studies require verification from sources other than the Principal Investigator.

17.1.1. Based on study progress information obtained from the Principal Investigator, the NMDP IRB may seek additional information from other sources or study staff. This shall include, but not be limited to, the following:

17.1.1.1. Adverse experiences.
17.1.1.2. Protocol deviations.
17.1.1.3. Stopping rules.
17.1.1.4. Enrollment.
17.1.1.5. Requests for additional products from the donor.

17.1.2. Complex projects involving unusual levels or types of risks to subjects.

17.1.3. Projects where there is concern that material changes occurred without IRB approval.

18. Continuing review

18.1. Continuing review of research studies will be conducted according to applicable regulations.

18.1.1. Studies subject to Pre-2018 Common Rule Requirements will undergo continuing review on an annual basis, unless a more frequent review interval is established for the research study at the time of the initial NMDP IRB review and approval.

18.1.2. Studies subject to 2018 Common Rule Requirements will undergo continuing review on an annual basis, unless the study is eligible for expedited review or has progressed to the point that the only remaining activities are data analysis, and/or accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care, unless the IRB determines otherwise.

18.1.3. Studies subject to the FDA regulations will undergo continuing review on an annual basis according to the current FDA requirements for IRB continuing review.

The continuing review should be conducted to ensure that:

18.1.4. Scientific goals and design of the study continue to be appropriate.

18.1.5. The informed consent document is accurate and complete, adequately describes the required procedures to participate in the study, and adequately describes the potential risks to the subject.

18.1.6. The review interval is still acceptable, or if necessary, a more frequent review interval will be established.

18.2. During the continuing review the IRB will determine whether significant new findings that may relate to a participant's willingness to continue taking part in the research study need to be provided to participants.

18.3. Continuing reviews shall be conducted if a study is open to enrollment, if the research remains active for long-term participant follow-up, or if the activities include analysis of identifiable private information. If the only remaining activity of a research project involves the analysis of aggregate data sets without individual subject identifiers, no further continuing review is necessary.

19. Data and Safety Monitoring Board (DSMB) reporting to the IRB

19.1. The IRB shall review statements and reports from DSMBs regarding the DSMB review of study-wide adverse events, interim findings, and any recent literature search.

19.2. If the NMDP IRB receives a DSMB report between continuing reviews, the report will be reviewed at the study's next continuing review, provided the DSMB recommended the study for continuation. If the DSMB cited any concerns in the report, the report will be reviewed by the NMDP IRB at the IRB's next regularly scheduled meeting.

19.3. The DSMB has the authority to:

19.3.1. stop a research study in progress,

19.3.2. remove individuals from the study, and

19.3.3. take any steps to protect the safety and well-being of participants until the IRB can assess.

20. Actions taken by the IRB

20.1. Research protocols undergoing initial or continuing review and protocol changes undergoing review are subject to the below-listed actions:

20.1.1. Approved: No changes are requested by the IRB; the investigator may initiate the study or continue the study, or may implement the changes to the protocol.

20.1.2. Approved with stipulations: Specific revisions are requested by the IRB before the research study may be initiated or continued beyond the current approval period, or before the protocol change may be implemented. The required revisions must be either administrative detail or meet one of the expedited review categories.

20.1.2.1. If all stipulations fall into the expedited review categories, then the primary and secondary reviewers, or their Chair-appointed designee, will be responsible for reviewing the response to stipulations and give final approval of the research.

20.1.2.2. If the stipulation only concerns an administrative detail (e.g., IRB approval letter from other participating institutions, etc.), the NMDP IRB staff may verify that the stipulation has been met.

20.1.3. Deferred: Substantive clarifications or modifications are required by the IRB before the research may be initiated or continued beyond the current approval period, or before the protocol change may be implemented. The convened IRB must review the response to the deferral. This includes stipulations which do not qualify for administrative review or meet one of the expedited review categories.

20.1.4. Disapproved: The research is not approved. The IRB shall provide the investigator with written notification of the reasons for disapproval. The investigator may appeal the IRB decision.

20.1.5. Suspended or terminated: The IRB has the authority to suspend or terminate previously approved research.

20.1.6. Tabled: If the convened IRB is unable to adequately review a study due to lack of time or loss of quorum, the study will be reviewed at the next full board meeting.

20.2. Investigators should respond in writing to IRB actions that require a response by the Investigator.

21. Stopping a study

21.1. When the Principal Investigator is closing a study, because the study has come to its natural conclusion or the study is being stopped early because of certain circumstances, the NMDP IRB must be notified. If a study has come to its natural conclusion, the Principal Investigator does not need to

immediately notify the NMDP IRB but can wait until the time of the study's continuing review with the NMDP IRB. If a study is stopped for any reason other than coming to a natural conclusion, the NMDP IRB must be notified immediately.

21.1.1. The NMDP IRB staff will review the submitted Notification of Study Closure form and determine if the study can be closed administratively, or if the information warrants further review by the NMDP IRB.

21.2. If the study was approved with stipulations at the time of continuing review, the IRB must accept the Principal Investigator's response to the IRB's conditions of approval by the date of IRB expiration. If this acceptance is not received by the time IRB approval expires, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions.

21.3. Continuing review documents must be reviewed and approved prior to the date of IRB expiration. If the review/approval does not occur prior to the expiration date, all research activities must stop, unless the IRB finds it is in the best interest of individual subjects to continue participating in the research interventions or interactions.

21.4. If a study does not receive final continuing IRB approval prior to the date of IRB expiration, the IRB will correspond with the Principal Investigator to determine whether there are currently enrolled participants with safety concerns or ethical issues that may arise if research activities are stopped, and whether the best interests of individual participants are served by continued involvement in the research.

22. Reviewing changes in approved research

22.1. If a Principal Investigator makes any changes to the NMDP IRB approved protocol or consent form, these changes must be approved by the NMDP IRB prior to the Principal Investigator implementing these changes except where necessary to eliminate any immediate hazards to the participants. These changes will be reviewed by the same criteria as those criteria used for the initial review. (See "Initial Review" section of this SOP.)

22.1.1. Any study changes implemented prior to NMDP approval in order to eliminate apparent immediate hazards to participants must be reported to the NMDP IRB no longer than within 30 days. Those changes will still be reviewed by the NMDP IRB to determine whether each change was consistent with ensuring the participant's continued welfare.

22.2. To ensure that no changes are made to an approved protocol or consent form without IRB approval, the NMDP IRB Notice of Action includes a directive that no modification may be made in the protocol or in the wording of the official consent form without prior approval of the IRB.

22.3. During review of changes in approved research the IRB will determine whether significant new findings that may relate to a participant's willingness

to continue taking part in the research study need to be provided to the participants.

22.4. **Certain administrative changes may be approved by NMDP IRB professional staff**. Examples of such administrative changes include:

22.4.1. Change in study title

22.4.2. Additional or changed contact names (other than the Principal Investigator) in consent or recruitment documents

22.4.3. Wording changes in the protocol, consent form, or other study documents simply to improve clarity, but that do not materially affect an assignment of the risks and benefits of the study or do not substantially change the specific aims or the design of the study.

22.5. **The following types of administrative changes may be made to documents without prior IRB approval,** as long as the Principal Investigator submits a tracked version of the modified document at the time of the next continuing review:

22.5.1. Corrections of grammatical or typographical errors or cut-paste errors

22.5.2. Additional or changed contact information (other than names) in consent or recruitment documents. For example, changing a phone number or adding an email address for research staff.

22.5.2.1. NOTE: A change in the actual contact process between research staff and study participants must be approved by the IRB prior to implementation. An example of this would be deciding to contact participants by telephone rather than just mailing them a letter.

22.6. Any questions regarding the review process for changes in previously approved research should be directed to NMDP IRB staff prior to implementing the changes.

23. Further review and approval of NMDP IRB actions within the NMDP

23.1. All research reviewed and approved by the NMDP IRB may be subject to further review by the Senior Management of the NMDP. However, NMDP Senior Management review is not required of any research reviewed and approved by the NMDP IRB.

23.2. If the NMDP Senior Management disapproves of a research study, this disapproval will override the NMDP IRB approval of the research study.

23.2.1. In such cases, the NMDP IRB will be informed of the NMDP Senior Management's disapproval of the study at the next regularly scheduled NMDP IRB meeting.

23.3. If the NMDP IRB disapproves a research study, the NMDP Senior Management may not override the NMDP IRB disapproval and approve the research study.

24. Department of the Navy (DON) review

24.1. Upon NMDP IRB approval, all NMDP research receiving DON funding must be submitted to the DON Human Research Protection Program for headquarters-level review.

24.2. Relevant NMDP IRB meeting minutes must also be submitted to DON.

24.3. DON review pertains to all review types (i.e., initial review, continuing review, and review of changes to previously approved research).

25. Appeal of IRB decisions

25.1. Criteria for appeal

25.1.1. Any member of the NMDP IRB may request review of a decision within two working days of the NMDP IRB's actions.

25.1.2. Any Principal Investigator may appeal an adverse decision of the NMDP IRB within one week of being notified of the NMDP IRB's actions.

25.2. Process for resolving the appeal

25.2.1. The appealing party shall make the request to the NMDP IRB Administrator for the NMDP IRB to reconsider their decision.

25.2.2. The Principal Investigator may present to the NMDP IRB information he/she feels is relevant to the appeal. The NMDP IRB members who originally reviewed the research study may also present information relevant to the appeal.

25.2.3. The NMDP IRB must resolve the appeal in a timely manner. Notice of action on the appeal will be sent to the Principal Investigator and the designated official at the Principal Investigator's institution.

26. Site-specific reviews for sites participating in the NMDP single IRB

26.1. <u>Review process for a site's enrollment in the NMDP single IRB</u>

26.1.1. Refer to S00038 *NMDP IRB Materials Required for Review* for materials that must be submitted by an institution to enroll in the NMDP single IRB.

26.1.2. Submissions of single IRB enrollment materials will be reviewed by NMDP IRB staff to ensure the institution has policies and procedures in place for overseeing and ensuring the safe and appropriate conduct of research at the institution.

26.1.2.1. If the information provided by the institution is not complete, sufficient, or needs clarification, IRB staff will correspond with the institution to obtain the information.

26.1.2.2. IRB staff may consult the NMDP IRB Administrator and/or NMDP IRB Chair for questions/concerns regarding the information submitted by the institution.

26.1.3. The IRB Authorization Agreement (IAA) will be forwarded electronically to the NMDP Institutional Official for signature.

26.1.4. IRB staff will send an email to the primary contact(s) at the institution notifying the institution that their enrollment in the NMDP single IRB is complete. Attached to the email will be the fully-signed IAA and the institution's boilerplate consent language approved by NMDP IRB staff.

26.2. Adding a research site as a relying institution under the NMDP IRB on a NMDP IRB-approved study

26.2.1. During the NMDP single IRB enrollment process, relying institutions attest that they confirm investigators are in good standing and authorized to conduct research at the institution prior to allowing the investigator to cede review of a study to an external IRB. This includes verification of the investigator's current training in human research protections. The relying institution also attests that they have a process for verifying that the institution has adequate resources (including space, equipment, and personnel) to conduct the study prior to allowing to cede to an external IRB.

26.2.1.1. If the institution does not maintain investigators' curriculum vitaes (CVs) or current medical licensures, these are obtained and reviewed by the central study-level Protocol Coordinator prior to activating a site on a study.

26.2.2. Refer to S00038 *NMDP IRB Materials Required for Review* for materials that must be submitted by a relying institution for the institution to open a study with the NMDP IRB.

26.2.3. NMDP IRB staff will review the submitted materials for completeness.

26.2.3.1. If the information provided is not complete, sufficient, or needs clarification, IRB staff will correspond with the institution to obtain the information.

26.2.4. NMDP IRB staff will compare the boilerplate language added to the study consent form with the institution's boilerplate language that was previously approved by NMDP IRB staff.

26.2.5. The submission to add the study site is considered a minor change to a previously-approved study and will be reviewed using the expedited procedure.

26.2.5.1. The NMDP IRB Chair or designee will review the submitted materials to assess the qualifications of the investigator, to assess the ability of the participating site to conduct the study, and to consider relevant local contextual factors for the participating site.

26.2.5.2. If for some reason the conduct of the study at the site would constitute a change in the criteria for approval (e.g., change in risks to subjects), the submission to add the study site would be reviewed by the convened IRB.

26.3. Reviewing changes to a study site's consent form

26.3.1. Refer to S00038 *NMDP IRB Materials Required for Review* for materials that must be submitted when changes have been made to the site's consent form.

26.3.2. If a site has revised their study consent form to include study-wide consent revisions that have already been approved by the NMDP IRB, the site's consent form will be reviewed and approved by the NMDP IRB staff administratively.

26.3.3. If a site has revised their study consent form to include changes to their institutional boilerplate consent language, the site's consent form will be reviewed and approved by the NMDP IRB staff administratively.

26.4. Reviewing translations of site-specific documents

26.4.1. Translated site-specific study documents such as consent forms or recruitment materials will be reviewed and approved by the NMDP IRB staff administratively.

26.4.2. NMDP IRB staff will verify the following:

26.4.2.1. The translated document matches with the corresponding NMDP IRB-approved English language document in:

26.4.2.1.1. Version number

26.4.2.1.2. Version date (if applicable)

26.4.2.1.3. NMDP IRB approval date (if applicable)

26.4.2.1.4. Study ID number

26.4.2.1.5. Study title

26.4.2.2. The Translator's Certificate of Accuracy or equivalent document corresponds to the translated document.

26.4.2.2.1. If a native speaker of the translation language performs the translation, another native speaker's verification of the translation may be accepted in lieu of a professional translator's Certificate of Accuracy at the NMDP IRB's discretion. (Refer to S00038 *NMDP IRB Materials Required for Review*)

26.5. Reviewing other site-specific changes for a study

26.5.1. Refer to S00038 *NMDP IRB Materials Required for Review* for materials that must be submitted for site-specific study changes.

26.5.2. If a study site makes other site-specific study changes (e.g., change in the site's Principal Investigator or revisions to other site-specific study documents), the change will be reviewed by the expedited procedure, provided it is considered a minor change to the previously approved study.

27. **Review of translated study-level documents**

27.1. Translated study-level documents such as consent forms or recruitment materials will be reviewed and approved by the NMDP IRB staff administratively.

27.2. NMDP IRB staff will verify the following:

27.2.1. The translated document matches with the corresponding NMDP IRB-approved English language document in:

27.2.1.1. Version number
27.2.1.2. Version date (if applicable)
27.2.1.3. NMDP IRB approval date (if applicable)
27.2.1.4. Study ID number
27.2.1.5. Study title

27.2.2. The Translator's Certificate of Accuracy or equivalent document corresponds to the translated document.

REFERENCES

1. 21 CFR 50 Protection of Human Subjects
2. 21 CFR 56 Subpart C
3. 21 CFR 312.2(b)
4. 21 CFR 812
5. 45 CFR 46.116
6. 45 CFR 46 Subpart A
7. 45 CFR 46 Subpart D
8. FDA Guidance: Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies
9. OHRP Guidance: Special Protections for Children as Research Subjects
10. SOP#: S00037, NMDP IRB Membership and Voting Requirements
11. SOP#: S00038, NMDP IRB Materials Required for Review
12. SOP#: S00041, NMDP IRB Expedited, Emergency, and Exempt from Regulation
13. Department of Defense Directive (DoDD) 3216.2
14. Department of Defense Dual Compensation Act 5 U.S.C. § 5531
15. Secretary of the Navy Instructions (SECNAVINST) 3900.39D
16. Department of Defense Instruction (DoDI) 3216.02

Revision History

Revision	Brief Description of Revision
S00040 08/17/2001	New SOP
S00040 version 2.0	Annual Review: Restructure content of SOP

Revision	Brief Description of Revision
S00040 version 3.0	Added a Definition. Added section 2. Updated sections 1, 3, 4, 5, 6, 10, 16, 17, and 22. Deleted former section 15 (Lapse in Approval). Formatting changes.
S00040 version 4.0	Added Section 15.2 regarding appointment of a medical monitor. Added Section 21 regarding Department of the Navy review.
S00040 rev 5	Put into new format. Added definition of consultant. Added 4.2, 6.1.2, 6.2.2, 6.2.3, 6.2.4, 6.2.5, 14.2, 14.3, 16.2, 17.4, 18.1.1, 18.3, and 20.2.1. Revised 20.1.
S00040 rev 6	Added definitions for Research protocol and Vulnerable subjects. Added 2.2 – 2.5, 5.1.1, 6.2.2, 6.2.3, 6.2.4.1, 6.2.7, 9.1.1.4, 9.1.5.1, 9.1.5.2, 9.1.6.1, 9.1.6.3, 9.1.6.4, . Added 4.3 and its subsections. Added 18.2.3 and its subsections. Added section 11 (Advertisements), section 12 (Research involving vulnerable subjects), and section 13 (Research involving investigational or unlicensed test articles). Deleted section 26.3.1. Clarifications made to a few other sections.
S00040 rev 7	Added sections 9.1.6.6, 12.1.1.1, 12.1.1.2, 12.1.1.3 and 12.1.2.2 and DoDI reference doc. Deleted sections 9.1.5.1 and 9.1.5.2. Deleted section 26 on reporting unanticipated problems. In Section 18 removed references to Dept of Navy requirements and independent medical monitor.
S00040 rev 8	Added 9.1.7 re: approval of research procedures contrary to NMDP Standards. Added 21.4 – 21.6 re: administrative changes to study documents. Updated Reference Documents
S00040 rev 9	Added section 12.3 re: benefit to the experimental subject for DoD-supported research Clarified section 21.1.1 as within 30 days
S00040 rev 10	Added section 12.1.2.1 stating that the primary reviewer will be responsible for providing the IRB with the protocol specific information supporting determinations made in accordance with 45 CFR 46 Subpart D that will be documented in the IRB meeting minutes.
S00040 rev 11	Added positions to definition of Senior Management. Revised definition of CIBMTR. Added Responsibilities section. Deleted mention of adverse event reports from 1.3 and 17.1. Added 8.2.2.1. Revised 12.2.2.2 and added 12.2.2.2.1. Added 20.1.1.
S00040 rev 12	Added definitions. Replaced DHHS with Common Rule. Revised section 16. Added sections 1, 1.1, 2.2, 11.2, 11.2.1, 11.2.2, 13.1.2, 13.1.2.2, 13.2.2.4, 18.1.1, 18.1.2, 18.1.3, 19.2, 26 and all its subparts, 27 and all its subparts. Added references.
S00040 rev 13	Added definition of IRBManager. Revised sect 4.1 and 4.2 to refer to IRBManager. Added section 6.3 regarding review of multi-site research. Added 15.1.1 regarding FDA determination of SR vs.

Revision	Brief Description of Revision
	NSR. Added section 26.4 on review of study-site translated documents.

ADDENDA

Not applicable