STANDARD OPERATING PROCEDURE

OBJECTIVE/SCOPE

To describe the responsibilities of the National Marrow Donor Program® (NMDP) Institutional Review Board (IRB) and other institutions when cooperative reviews of research are being conducted or when other institutions rely on the NMDP IRB.

MATERIALS

1. IRB Authorization Agreement

SAFETY

Not applicable

DEFINITIONS

1. **Be The Match BioTherapies℠:** A subsidiary of NMDP/Be The Match that focuses on partnering with organizations pursuing new life-saving treatments in cellular therapy

2. **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.

3. **BMT CTN Data and Coordinating Center (DCC):** Managed by three organizations (CIBMTR®, NMDP/Be The Match, and The Emmes Corporation), the DCC is responsible for maintaining continuity of operations and effective communications, data management, and statistical support for the BMT CTN.

4. **Center for International Blood and Marrow Transplant Research® (CIBMTR®):** A research collaboration between the National Marrow Donor Program®/Be The Match® and the Medical College of Wisconsin that facilitates critical observational and interventional research.

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. **Food and Drug Administration (FDA):** FDA is the federal agency responsible for ensuring that foods are safe, wholesome and sanitary; human and veterinary drugs, biological products, and medical devices are safe and effective; cosmetics are safe; and electronic products that emit radiation are safe. FDA also ensures that these products are honestly, accurately and informatively represented to the public.

7. **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.

8. **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.

9. **Lead IRB:** The lead IRB for a study reviews and approves all study documents prior to review/approval by participating study site IRBs. If a study site's IRB wishes to make substantive changes to any study documents, those changes must first be approved by the lead IRB and then re-distributed to study sites for approval by the sites' IRBs prior to implementation.

10. **Local context:** Significant contextual issues reflecting community norms, standards, and practices, or local culture and customs.

11. **Office for Human Research Protections (OHRP):** The United States government agency charged with oversight of protection of human research subjects.

12. **Reliance 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, usually referred to as an IRB Authorization Agreement.

13. **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.

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

15. **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.

16. **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.

RESPONSIBILITIES

Not applicable

PROCEDURE

NMDP IRB SERVING AS THE IRB OF RECORD

1. The NMDP IRB may serve as the IRB of record for the following:

   1.1. Sites participating in BMT CTN studies.

   1.2. Sites participating in NMDP or CIBMTR sponsored studies.

   1.3. Sites participating in industry-sponsored studies where CIBMTR or Be The Match BioTherapies is participating in some aspect of the study or in which CIBMTR or Be The Match BioTherapies has contract obligations.

   1.4. NMDP/Be The Match network member donor centers whose unrelated donors participate in transplant center initiated research protocols.

   1.5. Sites participating in studies other than the above where the NMDP IRB has been asked and agreed to serve as a single IRB for the study. Such studies must be in the field of hematopoietic cell transplantation.

2. The NMDP IRB will not serve as the IRB of record for institutions outside of the United States.

3. The NMDP IRB will not serve as a single IRB for federally-funded research that is not subject to the Cooperative Research provision as follows: 1) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or 2) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context. (45 CFR 46.114)

4. If the NMDP IRB is serving as the single IRB for a NIH-funded study, all participating sites are expected to rely on the NMDP IRB for the study, unless the site has requested and received an exception in accordance with NIH policy on exceptions from single IRB review.

5. If a study site wishes to rely on the NMDP IRB, the site must enter into an IRB Authorization Agreement (IAA) with the NMDP IRB. The IAA will clearly define the NMDP IRB responsibilities and the relying institution's responsibilities.

   5.1. The responsibilities listed in the IAA are required and non-negotiable. However, wording changes for clarification purposes may be made if agreed upon by both the NMDP IRB and the relying institution.

   5.2. If a site wishes to add a Component Institution or Affiliate Institution to an existing IAA, the IAA may be amended to include the institution, as long as the institution meets the definitions in the IAA of either a Component or Affiliate Institution.

   5.3. A site's existing IAA would not be amended to include additional research studies for that site. Rather, a new IAA would be created with the site specific to the additional study for which the site wishes to rely on the NMDP IRB.

   5.4. Should either party wish to terminate the IAA, the responsibilities specified in the IAA for both the NMDP IRB (as the IRB of record) and the relying institution will remain in effect until the relying institution's IRB is able to review the study.

6. The NMDP IRB, serving as the IRB of record, will take responsibility for all aspects of IRB review at the relying institution for the specific study. Unless required by the site's local IRB, it is not necessary for a relying institution to also obtain approval from their local IRB for the study.

7. All study-level NMDP IRB actions, determinations, and requirements will be communicated to relying institutions by the central study-level protocol team. All site-specific NMDP IRB actions, determinations, and requirements will be communicated to the site by the NMDP IRB staff.

8. For research that falls within the scope of the NIH Genomic Data Sharing (GDS) Policy, the submitting institution is responsible for meeting the certification requirements of the GDS Policy. The NMDP IRB will be responsible for reviewing the investigator's proposal for data submission and the informed consent materials in accordance with the GDS Policy.

9. **Responsibilities of the NMDP IRB as the IRB of Record**

   9.1. Conduct initial, amendment, and continuing reviews of the protocol, informed consent documents, and any other study-specific documents for the study.

   9.2. Make the determinations regarding requirements for obtaining assent and documentation of assent for studies involving children as subjects.

   9.3. Conduct review of local context considerations. Local review will be assessed through a questionnaire completed by the relying institution or by other means, such as the relying institution's NMDP/Be The Match Network membership agreement.

9.4. Conduct review of unanticipated problems when the relying institution or other entity reports an incident, experience, or outcome that might be considered an unanticipated problem involving risks to participants or others. (Refer to S00407 *Unanticipated Problems Involving Risks to Participants or Others* for the management of reports of potential unanticipated problems.)

9.5. Conduct review of serious and/or continuing non-compliance when the relying institution or other entity reports an incident of potential serious or continuing non-compliance. (Refer to S00213 *NMDP IRB Managing and Reporting Non-Compliance with Human Research Protection Program Requirements* for the investigation and management of allegations of non-compliance.)

9.6. Report determinations of serious and/or continuing non-compliance and determinations of unanticipated problems involving risks to participants or others to OHRP, FDA or other applicable agencies. For research subject to the 2018 Revised Common Rule Requirements, such reporting to OHRP will only occur for federally-funded studies.

9.7. If applicable, provide institution-specific documents related to the NMDP IRB review by email to research staff and institutional designees.

9.8. Upon request, provide NMDP IRB Standard Operating Procedures and IRB membership roster to the relying institution.

9.9. The NMDP IRB has the authority to suspend or terminate approval of all or part of the research study at the relying institution that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to participants. The NMDP IRB will report such suspensions or terminations to BMT CTN DCC (if applicable), OHRP, FDA or any other applicable agency. For research subject to the 2018 Revised Common Rule Requirements, such reporting to OHRP will only occur for federally-funded studies.

9.10. Review any researcher or research staff financial conflict of interest (FCOI) management plans submitted by the relying institution and decide whether the management plan for the conflict allows the research to continue at the relying institution.

9.11. Request additional approvals from DHHS, if necessary, when the research involves pregnant women, fetuses, and neonates.

10. Responsibilities of the Relying Institution

10.1. Comply with all NMDP IRB actions, determinations and requirements regarding the study.

10.2. Comply with NMDP IRB policies and procedures.

10.3. Provide the NMDP IRB with any local context issues relevant to the research protocol.

10.4. Research may be further reviewed and approved or disapproved by officials of the relying institution, but they may not approve the research if it has not been approved by the NMDP IRB.

10.5. Cooperate with the NMDP IRB for all reviews, record keeping and reporting, and provide information requested by the NMDP IRB in a timely manner.

10.6. The relying institution and its researchers acknowledge that they are primarily responsible for safeguarding the rights and welfare of each research participant, and that the participant's rights and welfare must take precedence over the goals and requirements of the research.

10.7. Oversee the conduct of the study at their institution. This includes, but is not limited to:

10.7.1. Monitoring protocol compliance;

10.7.2. Maintaining compliance with state, local, or institutional requirements related to the protection of human subjects;

10.7.3. Initiating changes in the research only after NMDP IRB review and approval, except where necessary to eliminate apparent immediate hazards to the participants;

10.7.4. Enrolling individuals in the research only after NMDP IRB review and approval;

10.7.5. Obtaining, documenting, and maintaining records of consent for each participant or each participant's legally authorized representative as stipulated by the NMDP IRB;

10.7.6. Providing a mechanism to receive and address questions, concerns, and complaints from local study participants and others about the conduct of the research;

10.7.7. Notifying the NMDP IRB of any study-specific incident, experience or outcome that rises to the level of an unanticipated problem involving risks to participants or others and/or potential serious or continuing non-compliance. At the time the incident, experience or outcome is reported to the NMDP IRB, the relying institution must also provide a plan to manage it.

10.8. For studies that are **not** federally-funded, the relying institution is responsible for reporting the following to applicable federal agencies (if applicable according to the relying institution's policies and procedures): 1) NMDP IRB determinations of unanticipated problems involving risks to participants or others, 2) NMDP IRB determinations of serious and/or continuing non-compliance, and 3) NMDP IRB's suspension or termination of all or part of the study at the relying institution.

10.9. Manage organizational conflicts related to the study.

10.10. Obtain disclosures of and manage financial conflicts of interest (FCOI) of researchers and research staff at the relying institution. Provide conflict of interest management plans to the NMDP IRB.

10.11. Ensure researchers and research staff at the relying institution comply with education and continuing education requirements of the relying institution.

10.12. Ensure compliance with applicable Health Insurance Portability and Accountability Act (HIPAA) privacy regulations. This includes making determinations as required by and in compliance with the HIPAA Privacy Rule for use and disclosure of protected health information (PHI) for the research, including waivers of, or alterations of authorizations.

10.13. Conduct other ancillary reviews required by the protocol or by the institution (e.g., scientific review, biosafety, radiation safety, etc.)

10.14. Conduct IRB review in accordance with Subpart C of 45 CFR 46 and request additional approvals from DHHS when the research involves prisoners. The NMDP IRB is not constituted to review research involving prisoners.

10.15. Make no language changes to the NMDP IRB-approved informed consent documents for sections that apply to:

10.15.1. Study invitation and introduction

10.15.2. Study background

10.15.3. Study purpose

10.15.4. Study procedures, treatment and tests

10.15.5. Participant risks and discomforts

10.15.6. Possible participant benefits

10.15.7. If the institution wishes to make any changes to the language in the above listed sections, the language changes must be submitted to the NMDP IRB for review and approval. To create the institutional informed consent documents, the institution must use the NMDP IRB-approved consent form template. The institution may insert the institutional boilerplate language that was submitted as part of the local context review, and approved by the NMDP, into the NMDP IRB-approved consent form template. The institution may add their institution's logo to the consent form.

10.16. Prior to implementation, submit the institutional informed consent documents for review to the central study-level protocol team.

10.17. For transplant center-initiated research, NMDP/Be The Match donors will sign the consent form approved by the NMDP IRB. Donor centers that rely on the NMDP IRB

may put the consent form on their own institution's letterhead; however, no content changes may be made to the form.

NMDP IRB SERVING AS A LEAD IRB IN MULTI-SITE STUDIES

11. The NMDP IRB serves as the lead IRB for all NMDP/CIBMTR sponsored studies.

12. All NMDP IRB actions, determinations, and requirements regarding a study for which the NMDP IRB serves as the lead IRB will be communicated to study sites by the central study-level protocol team.

13. **Responsibilities of the NMDP IRB as the Lead IRB**

13.1. Conduct initial, amendment, and continuing reviews of the protocol, informed consent document templates, and any other study-specific documents for the study prior to local IRB reviews at study sites.

13.2. The NMDP IRB has the authority to suspend or terminate approval of NMDP/CIBMTR sponsored research. The NMDP IRB will report such suspensions or terminations according to S00399 *Suspension, Termination and Administrative Closure of Research.*

14. **Responsibilities of Study Sites When the NMDP IRB Serves as the Lead IRB**

14.1. Be responsible for all aspects of IRB review at the participating site for the specific study, unless the site enters into an IAA with the NMDP IRB for the study.

14.2. Each participating site's IRB shall make the determinations for their own site regarding the requirements to obtain assent and documentation of assent for studies involving children as subjects.

14.3. Follow their own institutional policies and procedures for managing and reporting to the applicable federal agencies any unanticipated problems involving risks to participants or others or serious and/or continuing non-compliance that occurs at their institution.

14.3.1. Report determinations of unanticipated problems involving risks to participants or others and determinations of serious and/or continuing non-compliance to the central study-level protocol team.

14.4. Oversee all aspects of the conduct of the study at their institution.

14.5. Make no language changes to the NMDP IRB approved informed consent documents for sections that apply to:

14.5.1. Study invitation and introduction

14.5.2. Study background

14.5.3. Study purpose

14.5.4. Study procedures, treatment and tests

14.5.5. Participant risks and discomforts

14.5.6. Possible participant benefits

14.5.7. If the institution wishes to make any changes to the language in the above listed sections, the language changes must be submitted to the NMDP IRB for review and approval. To create the institutional informed consent documents, the institution may format the documents according to institutional preferred format and merge the institutional boilerplate language with the NMDP IRB approved study-specific language.

14.6. Prior to implementation, submit the institutional informed consent documents for review to the central study-level protocol team.

14.6.1. Exceptions to this are the CIBMTR Research Database and CIBMTR Research Sample Repository studies. These studies are not treatment/intervention-related protocols. Although participating sites must submit their informed consent documents to the central study-level protocol team for review, sites may begin using their informed consent documents for these two studies prior to the central study-level protocol team's review, provided they have been approved by the site's local IRB.

COOPERATIVE IRB REVIEWS FOR TRANSPLANT CENTER INITIATED RESEARCH PROTOCOLS

15. Responsibilities of the NMDP IRB in Transplant Center Initiated Studies

15.1. Conduct initial, amendment, and continuing reviews of the protocol, unrelated donor informed consent documents, and any other study-specific documents for protocol procedures that relate to NMDP/Be The Match unrelated donors.

15.1.1. The NMDP IRB review of the study solely for the protection of the rights and welfare of Be The Match unrelated donors will be documented on the Notice of Action (approval letter).

15.2. Create the informed consent document(s) for NMDP/Be The Match unrelated donors.

15.3. Provide a process for obtaining consent from unrelated donors and communicating donor decisions to the transplant center.

15.4. Follow NMDP policies and procedures for managing and reporting any unanticipated problems involving risks to participants or others or serious and/or continuing non-compliance that occurs at the NMDP or NMDP/Be The Match donor centers.

16. **Responsibilities of the Transplant Center and Primary Investigator**

16.1. Be responsible for all aspects of IRB review of protocol procedures that relate to any study subjects other than NMDP/Be The Match unrelated donors.

16.2. Make the determinations regarding the requirements to obtain assent and documentation of assent from any study subjects who are children.

16.3. Follow their own institutional policies and procedures for managing and reporting to the applicable federal agencies any unanticipated problems involving risks to participants or others or serious and/or continuing non-compliance that occurs at their institution.

16.4. Oversee all aspects of the conduct of the study at their institution, including obtaining consent from any study subjects other than NMDP/Be The Match unrelated donors.

16.5. Track subject enrollment, including enrollment of NMDP/Be The Match unrelated donors.

NMDP RELYING ON AN EXTERNAL IRB

17. Circumstances in which the NMDP may rely on an external IRB include, but are not limited to, the following:

17.1. Use of the Central Institutional Review Board for the National Cancer Institute (NCI CIRB) is required.

17.2. The study is a federally-funded multi-site study, where the use of a single IRB is required, and the NMDP IRB is not serving as the single IRB for the study.

17.3. The principal investigator or research consortium is mandating the use of a single IRB, and the NMDP IRB is not serving as the single IRB for the study.

17.4. An external IRB has particular expertise, not found on the NMDP IRB, for reviewing a particular study.

17.5. Determining that NMDP IRB review is not feasible due to lack of resources, legal concerns, institutional conflicts of interest, or other concerns.

18. NMDP will only rely on an external IRB that is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

19. Refer to S00038 *NMDP IRB Materials Required for Review* for materials that must be submitted to the NMDP IRB to request to cede IRB review of a study to an external IRB.

20. The NMDP IRB Administrator will determine whether or not to grant a request to rely on an external IRB.

20.1. The NMDP IRB Administrator will:

20.1.1. Review the submitted Request to Rely on an External IRB form.

20.1.2. Verify the NMDP/Be The Match personnel involved in the research are current with their human research protections training requirements, including training on this standard operating procedure.

20.1.3. Review the Financial Disclosure Forms submitted for each NMDP/Be The Match personnel involved in the research.

20.1.3.1. If any of the personnel disclose a significant financial interest in the research, the form will be forwarded to the Office of General Counsel to determine a management plan.

20.1.3.2. The investigator and research team must comply with any resulting conflict of interest management plans.

20.1.4. Verify with the Office of General Counsel that there are no institutional conflicts of interest with the research.

21. The study must not be submitted to the external IRB until the request to rely on an external IRB has been granted.

22. If the request to rely on an external IRB is granted, an IRB Authorization Agreement (IAA) must be signed by both the NMDP and the external IRB.

22.1. Either the NMDP's IAA template or the external IRB's IAA template may be utilized, as long as the division of responsibilities is clearly delineated and agreed upon by both parties. The IAA must include which party is responsible for reporting suspensions, terminations, and determinations of serious non-compliance, continuing non-compliance, or unanticipated problems involving risks to participants or others to federal agencies, when applicable.

23. The person who signs the *Request to Rely on an External IRB form* is responsible for providing the external IRB with any requested local context information.

23.1. Local context information is NMDP-specific information that is relevant to the study (e.g., state or local laws and regulations or institutional policies relevant to the protection of human research participants).

23.2. This information may also include NMDP-specific language required in approved consent documents, such as local contacts for research participants' questions.

23.3. The NMDP IRB office may be consulted regarding the local context information provided to the external IRB.

24. NMDP officials may not approve the research if it has not been approved by the external IRB.

25. The investigator and research team's responsibilities include:

25.1. Providing the NMDP IRB with copies of all approvals and determinations made by the external IRB for the study.

25.2. Complying with the determinations and requirements of the external IRB.

25.3. Notifying the external IRB when local context/policies that impact IRB review are updated.

25.4. Cooperating in the external IRB's reviews of the study, record keeping, and reporting. All information requested by the external IRB must be provided in a timely manner.

25.5. Reporting promptly to the external IRB any proposed changes to the research. Changes may not be implemented (including changes in the consent document) without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the participants.

25.6. Ensuring participants are not enrolled in the research prior to review and approval by the external IRB and prior to the meeting of any/all other applicable requirements and approvals for the study.

25.7. Ensuring that consent is obtained and documented for each participant or each participant's legally authorized representative (per the external IRB's determinations) and that records of consent are maintained.

25.8. Reporting promptly to the external IRB any unanticipated problems involving risks to participants or others according to the requirements specified in the IAA.

25.9. Reporting non-compliance, participant complaints, protocol deviations or other events according to the requirements specified in the IAA.

25.10. Providing the NMDP IRB with copies of any reports of serious non-compliance, continuing non-compliance, and unanticipated problems involving risks to participants or others that were submitted to the external IRB.

25.10.1. These reports must be submitted to the NMDP IRB at the same time that they are submitted to the external IRB.

25.10.2. The investigator must submit to the NMDP IRB the resulting determinations of the external IRB's review of these reports.

25.11. Providing to the external IRB data safety monitoring reports according to the external IRB's reporting policy.

25.12. Conducting monitoring in addition to, or in cooperation with, the external IRB, when appropriate.

REFERENCES

1. 45 CFR 46
2. NIH Genomic Data Sharing (GDS) Policy
3. NIH Policy on the Use of a Single IRB for Multi-Site Research
4. S00038 NMDP IRB Materials Required for Review
5. S00213 NMDP IRB Managing and Reporting Non-Compliance with Human Research Protection Program Requirements
6. S00399 Suspension, Termination and Administrative Closure of Research
7. S00407 Unanticipated Problems Involving Risks to Participants or Others

Revision History

Revision	Brief Description of Revision
S00592 rev. 1	New SOP
S00592 rev. 2	Deleted 5.5.1 that stated the BMT CTN DCC would report non-compliance to OHRP. Deleted statement in section 6 that said the BMT CTN DCC would report suspensions/terminations to OHRP. Added 7.2, 7.6, and 7.7. Elaborated on subsections of 7.8 and added clarifications to 7.8.7. Elaborated on subsections of 11.5.
S00592 rev. 3	Deleted 5.4.1 and 5.4.2. Section 5.5.1 was revised and became 5.6. Revised 6 and added 7. Added 8.3., 8.4., and 8.5.3. Revised 8.7 and added 8.8.
S00592 rev. 4	Added definitions of Be The Match BioTherapies and Common Rule. Added sections 2.1, 2.2, and 2.3. Added 8.4, 8.6, 8.73, and 8.74 and clarified 8.9 and 8.11 to be consistent with the terms of the IRB Authorization Agreement. Added entire section on NMDP Relying on an External IRB. Added references. Deleted reference to S00412. Clarified OHRP reporting requirements.

S00592 rev. 5	Added 1.3.
S00592 rev. 6	Added definition of Single IRB. Removed requirements for a Memorandum of Understanding for TC-initiated research studies. Used "central study-level protocol team" to replace references to Emmes Corp, etc. Added 13.1.1 to note that IRB jurisdiction solely for Be The Match unrelated donors in TC-initiated studies will be documented on the Notice of Action.
S00592 rev. 7	Added 1.5 regarding other studies not falling into the categories above it. Added sections 2 and 3 regarding when the NMDP IRB will not serve as a single IRB. Added sect 4 regarding exceptions on the NIH single IRB review policy. Added 5.4 regarding termination of IAA. Added sect 8 regarding the GDS Policy. Added 9.11 regarding additional approvals from DHHS for pregnant women. Added 10.8 regarding relying institution's reporting requirements for non-federally-funded studies. Added 10.14 regarding IRB review and approvals for research involving prisoners. Added investigator responsibilities in section 25.

ADDENDA

Not applicable