

NATIONAL MARROW DONOR PROGRAM®

**PROTOCOL FOR A RESEARCH SAMPLE
REPOSITORY**

FOR

**ALLOGENEIC
HEMATOPOIETIC STEM CELL
TRANSPLANTATION
AND MARROW TOXIC INJURIES**

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1. Background

1.1 *National Marrow Donor Program*

The National Marrow Donor Program[®] (NMDP) was established in 1986 as the result of a Federal contract that was awarded to create and maintain a registry of volunteer hematopoietic stem cell (HSC) donors. Physicians search the NMDP Registry on behalf of patients in need of an HSC transplant who have no suitably matching related donor. In 1999 the NMDP added a Cord Blood Registry to provide more donor source options for patients in need of an unrelated HSC transplant. At the end of December 2008, the NMDP Registry listed more than 7.5 million volunteer donors, 28,000 cord blood units (CBU), and had facilitated over 35,000 unrelated HSC transplants. In 2006, the NMDP was awarded a subcontract by the Medical College of Wisconsin to serve as the Related Transplant Research Repository for the Stem Cell Therapeutic Outcomes Database (SCTOD). The Medical College of Wisconsin – Center for International Blood and Marrow Transplant Research (CIBMTR) holds the federal contract to operate the SCTOD.

1.2 *Establishment and Purpose of the NMDP Research Sample Repository*

In 1987 the NMDP established the NMDP Research Sample Repository which is currently located at the NMDP Repository Services facility in New Brighton, Minnesota with a backup location at the Coriell Institute for Medical Research in Camden, New Jersey. The primary objective of this repository is to make blood samples available for research studies related to histocompatibility and HSC transplantation. Blood samples are donated by donors, CBUs and recipients who have registered, donated or received an allogeneic HSC transplant covered under the C. W. Bill Young Transplantation Program. As of May 2009, there are over 46,000 unique blood samples in the NMDP Research Sample Repository.

The NMDP Research Sample Repository maintains updated standard operating procedures (SOP) for all aspects of operation including but not limited to: sample receipt, sample handling, sample culture, sample labeling, sample storage and sample retrieval and shipment.

The following are types of studies that the NMDP allows the samples to be used for without obtaining additional consent from the recipient. Studies to:

- Improve the understanding of tissue matching for HSC donors and recipients;
- Determine and evaluate the factors that affect transplant outcome;
- Study the distribution of HLA tissue types in different populations; e.g., study tissue typing differences between different racial and ethnic populations to help develop methods to improve tissue matching between donors and recipients, including testing of rare HLA types.
- Use for delinked (anonymous) research.

2. Eligibility to Participate in the NMDP Research Sample Repository

2.1 Hematopoietic Stem Cell Donors

Donors are eligible to participate in the NMDP Research Sample Repository if they have donated or are scheduled to donate HSCs to an allogeneic recipient either by a marrow harvest or by apheresis.

Registered volunteer donors are eligible to participate in the NMDP Research Sample Repository if selected for further tissue type characterization in research projects designed to enhance the NMDP search (match) algorithm. Search algorithm enhancement research will entail potential donor match identification, verification of donor tissue type (including rare tissue types) and analyses to further characterize factors that impact histocompatibility. A tissue type is considered rare if it has been found in less than one in a million donors on the NMDP registry. Donors with rare tissue types will be targeted based on HLA typing results reported to the NMDP.

2.2 Cord Blood Units

Testable material from CBUs (Specimens) infused at transplant centers covered under the C. W. Bill Young Transplantation Program are eligible for inclusion in the NMDP Research Sample Repository. Material may be submitted by participating transplant centers, centralized laboratories and CBBs.

2.3 Hematopoietic Stem Cell Recipients

All U.S. recipients of allogeneic HSC transplants are eligible to participate in the NMDP Research Sample Repository.

2.4 Individuals with Marrow Toxic Injury

Any individual who is treated for a marrow toxic injury at a center participating in the NMDP's Radiation Injury Transplant Network (RITN) is eligible to participate in the NMDP Research Sample Repository. This includes adults with and without decision-making capacity and children. Eligible individuals may have received support care only, growth factor support, HSC transplant or other appropriate medical treatment for marrow toxic injury. Treatments applied are at the discretion of the care facility, and are not determined by the NMDP or CIBMTR.

2.5 Informed Consent to Participate in the NMDP Research Sample Repository

All participants, with the exception of CBU specimens, will be provided information about participation in the NMDP Research Repository and must sign an Institutional Review Board (IRB) approved informed consent document indicating their consent to participate in the repository. Documentation of assent and of parent legal guardian permission of minor participants, and consent for adult participants, must be maintained at the center where the participant or their parent or legal guardian provided consent to participate.

2.5.1 Minor Assent

- Adequate provisions must be made for soliciting and documenting assent of the children and permission of their parents or legal guardians, as set forth in 46.408.
- The research procedures do not involve more than minimal risk; therefore assent will be sought from all minors 7 to 17 years of age capable of providing assent.
- Age appropriate information will be provided to minors 7 to 11 years of age and minors 12 to 17 years of age.
- Local Institutional Review Boards will be responsible for determining how assent will be documented.
- The research in this protocol is covered by 45 CFR 46.404; therefore the written permission of the parent or legal guardian is required.
- The minor may only participate in the research if the minor and a parent or legal guardian agree to the minor's participation. If either the parent or the minor declines participation in the study, the minor shall not be enrolled in the study. If the minor lacks the capacity to provide assent, parent or legal guardian permission is sufficient.

2.5.2 Cord Blood Specimens

- Specimens obtained from a CBU used for transplant do not involve human subjects according to the Office for Human Research Protections guidance released August 10, 2004 entitled, "Guidance on Research Involving Coded Private Information or Biological Specimens" by virtue of meeting the following criteria:
 - The specimens were not collected specifically for inclusion in the NMDP Research Sample Repository and related research activities, but rather for use in transplantation.
 - The NMDP, transplant centers and centralized laboratories cannot readily ascertain the identity of the specimen donors because the coded identifying information key is held by the CBB and will not be shared with the NMDP

3. IRB Approval Process for Research Sample Repository

All transplant centers and donor centers must have an IRB-approved protocol and consent forms prior to submitting recipient and donor blood samples to the Research Repository. The center's designated IRB may not waive informed consent requirements under this protocol. Recipients and donors must provide informed consent for submission of blood samples to the Research Repository.

Local IRB review and approval is necessary except in the case of donor centers that designate the NMDP IRB as their IRB. Centers must use the protocol and

consent forms provided by the NMDP and submit them to their designated IRBs for review and approval.

The process for local and NMDP IRB approval are as follows:

- The NMDP's template protocol and consent forms may be modified to include the name of the local institution, local institutional contact, and to conform to other similar non-substantive format or content changes required by the center's designated IRB.
- The modified template protocol and consent forms must be reviewed and approved by the center's designated IRB.
- Any substantive changes to the protocol or consent forms suggested or stipulated by the local IRB need to be reviewed and approved by the NMDP IRB.
- The IRB approval letter and the IRB-approved protocol and consent forms must be submitted to the IRB Office at the NMDP.
- Centers may begin submitting blood samples as soon as the site's Principal Investigator notification from NMDP IRB Staff acknowledging that an IRB-approved protocol and consent form is in place at the center.
- The above process is followed for each continuing review period. If there is a lapse in IRB approval, the center will not be allowed to submit blood samples to the NMDP until IRB-approval has been obtained.
- In cases where the center has designated the NMDP IRB on their center's FederalWide Assurance, and an IRB Authorization Agreement is in place for the Research Repository protocol, the center does not need to obtain any additional IRB approval.

4. Collection of Samples

4.1 Collection of Donor and Recipient Blood Samples

Blood samples should be collected as indicated on the NMDP Research Repository Critical Facts Sheet.

4.1.1 Unrelated Donor Transplants

Recipient samples are collected prior to the recipient starting the preparative regimen for the transplant. Twenty milliliters (20 mL) of blood are collected from adult recipients. For pediatric recipients where the collection of the full sample is medically contraindicated, as little as one milliliter (1 mL) of blood may be collected.

Unrelated donor samples are collected either prior to the HSC collection or after the collection, whichever is the most convenient and safe for the donor. Samples from registered volunteer donors with rare tissue types will be collected at the donor's convenience any time after registration. For all donors, 20 milliliters (20 mL) of blood are collected.

In cases where donor or recipient blood samples are not available, samples may consist of any material that could potentially yield testable DNA. Types may include red cell pellets, extracted DNA, dried blood on filter paper, viable cells, and any other testable material.

4.1.2 Related Donor Transplants

Recipient samples are collected prior to the recipient starting the preparative regimen for the transplant. Ten milliliters (10 mL) of blood are collected from adult recipients. For pediatric recipients where the collection of the full sample is medically contraindicated, as little as one milliliter (1 mL) of blood may be collected.

Related donor samples are collected either prior to the HSC collection or after the collection, whichever is the most convenient and safe for the donor. For all donors, 10 milliliters (10 mL) of blood are collected.

In cases where donor or recipient blood samples are not available, samples may consist of any material that could potentially yield testable DNA. Types may include red cell pellets, extracted DNA, dried blood on filter paper, viable cells, and any other testable material.

4.1.3 Individuals With Marrow Toxic Injury

Samples are collected prior to the individual starting a preparative regimen if a transplant is directed. Otherwise, samples are collected whenever convenient and safe for the individual. Twenty milliliters (20 mL) of blood are collected from an adult. For pediatric individuals, where the collection of the full sample is medically contraindicated, as little as one milliliter (1 mL) of blood may be collected.

In cases where blood samples are not available, samples may consist of any material that could potentially yield testable DNA. Types may include red cell pellets, extracted DNA, dried blood on filter paper, viable cells, and any other testable material.

4.1.4 Donors for Tissue Type Characterization and Algorithm Enhancement

Samples from registered volunteer donors with rare tissue types are collected after registration at a time convenient and safe for the donor. Up to fifty milliliters (50 mL) of blood are collected from an adult.

In cases where blood samples are not available, samples may consist of any material that could potentially yield testable DNA. Types may include red cell pellets, extracted DNA dried blood on filter paper, viable cells, and any other testable material.

4.2 Collection of CBU Specimens

CBU specimens may consist of any material remaining at the Cord Blood Bank, Transplant Center, or NMDP Confirmatory Typing Laboratory that could potentially yield testable DNA. Specimen types include red cell pellets, extracted DNA, dried blood on filter paper, viable cells, and any other testable material.

5. Sample Processing

5.1 Cell Storage

Donor and recipient samples are stored as whole blood and plasma. These samples are stored in liquid nitrogen and/or –80°C freezer or as dried blood on filter paper. These samples are processed and stored according to standard operating procedures. Cord blood specimens are received and stored frozen.

5.2 Cell Transformation

An attempt is made to generate an Epstein-Barr Virus (EBV)- transformed B-Lymphoblastoid Cell Line (B-LCL) on donor and recipient samples as needed to replenish inventory. B-LCLs provide a renewable source of DNA. Cell lines are developed according to standard operating procedures. No attempts are made to transform cord blood material because of the limited volume and absence of an effective procedure.

5.3 Cell Expansion

Transformed cells may be expanded in culture to replenish depleted inventory stores.

5.4 Vial Labeling

Samples are labeled with an identification number that includes no identifying information assigned to the donor, recipient or CBU and the date the sample was prepared and frozen.

6. Duration of Sample Storage at the NMDP Research Repository

Research samples will be stored at the repository until the material has been exhausted or the repository is discontinued. The NMDP/CIBMTR is the custodian of all samples in the Research Repository and may at its discretion destroy samples that it determines should not be retained. NMDP may transition responsibility to another custodian that meets all necessary requirements. If the repository is permanently closed all stored sample material will be destroyed.

Samples may be maintained beyond the death of the participant. In this case, samples will only be used for the histocompatibility related studies or completely anonymous research studies outlined in the “Use of Research Repository Samples” section below.

7. Access to Samples

7.1 Who May Request Access to Samples

Representatives of participating centers and investigators or research groups may request access to research samples contained in the NMDP Research Sample Repository for the purpose of conducting research. Medical Directors and Coordinators from the NMDP network may request and be provided samples collected by their own centers, provided there are sufficient aliquots in the Repository to do so.

7.2 How Requests Are Reviewed/Approved

Samples are released according to policies established and maintained by the NMDP/CIBMTR. Briefly, requests are reviewed by NMDP/CIBMTR staff who determine if committee approval is needed to release the sample(s). Participating centers requesting samples from subjects from their own center for the specific purpose of treating a donor or a patient do not need committee approval to access the samples. Requests for samples for use in a research study that includes correlation with clinical outcome data must be reviewed and approved for scientific merit by a CIBMTR Working Committee. Following CIBMTR committee approval, the Repository Oversight Committee must approve the release of the samples for the study. If the study is scientifically sound, the NMDP IRB Chair performs an administrative review of the study protocol to ensure that it is within the limits defined in the Research Repository protocol and is covered by the participant's informed consent document for the Research Repository. Requests for samples for use as reference or quality control material must be reviewed and approved by the Repository Oversight Committee and the NMDP IRB Chair prior to release of the samples.

8. Use of Research Repository Samples for Research Studies

The NMDP IRB Chair will administratively review each study proposal after it has been approved for scientific merit. If the NMDP IRB Chair determines that the study proposal falls within one of the listed categories of research, then consent beyond the initial consent obtained from the Repository participant is not necessary nor is full committee review.

8.1 Linked Research

Linked research is any research where a mechanism exists to trace data or samples back to the identity of the research subject. This includes any of the following research that investigates factors influencing the outcomes of unrelated donor HCT:

- Studies of histocompatibility including HLA typing, analysis of allele and haplotype frequencies in different populations, evaluation of microsatellites and single nucleotide polymorphisms, examination of minor histocompatibility antigens, or other factors known or found to be involved in donor / recipient histocompatibility.

- Studies of immune regulatory systems including interleukins, interferons, tumor necrosis factors and others as these may influence the outcomes of transplantation.
- Studies of molecules involved in natural defense systems such as myeloperoxidases, oxidative enzymes, perforins, defensins, adhesion molecules and others.
- Studies of other molecules that may influence the outcomes of transplantation including coagulation factors and coagulation regulators, platelet and endothelial cell functional and regulatory systems, complement systems, and others.
- Studies of molecular systems known or found to be involved in the proliferation or maintenance of hematopoietic and immune systems including growth factors, cell surface and cytoplasmic receptors, cell cycle regulators, DNA and gene regulatory molecules, DNA telomeres, and others.

8.2 Delinked (Anonymous) Research

Delinked (anonymous) research is research where it is impossible under any circumstances to trace data or samples back to the identity of the research subject. Any research project may be proposed for anonymous research. Such projects follow the process for review and approval as outlined in Section 7.2.

- Samples provided for anonymous research will have identifiers removed and replaced with appropriately designed, non-traceable serial numbers.
- Subject to the “Data Available with Samples” section below, samples may be combined with outcome data from NMDP/CIBMTR databases prior to anonymization. In such instances, all personal identifying information including names, ID numbers, birthdates, addresses, admission dates, hospitalization sites, etc. will be removed. Personal identifiers deemed necessary for the research, e.g., zip codes, will only be provided following NMDP IRB approval.

8.3 Studies Outside the Scope of this Protocol

In cases where an investigator proposes research that does not fall under the guidelines set forth in the “Use of Research Repository Samples” section above, the proposal will be reviewed for scientific merit according to NMDP/CIBMTR policies. If approved based on the scientific merit, the study will be subject to IRB review and approval, including a determination of the requirements for additional informed consent, if any.

8.4 Data Available With Samples

Research studies using Research Repository samples may include data from the NMDP/CIBMTR research databases, subject to provisions of the research database protocol and NMDP policies and procedures.

8.5 Restrictions on Sample Usage at the Investigative Site

- The intended use for the Research Repository samples is to facilitate research projects.
- Commercial use of samples from the NMDP Research Sample Repository is strictly forbidden without the prior written consent of the NMDP.

- Third-party distribution of any of the samples from the NMDP Research Sample Repository is strictly forbidden without the prior written consent of the NMDP.
- Upon request, the requestor shall return to the NMDP any samples obtained from the Research Sample Repository.
- After testing is complete, samples must be disposed of according to local and state biohazardous waste laws.
- Samples must not be retained indefinitely.
- Requestor will not receive any identifying information with the samples that could possibly be used to link the sample to the contributing individual.

9. Participant Withdrawal from the Research Sample Repository

At any time either a recipient or donor may request that his or her sample be removed from the Research Sample Repository. The recipient or donor may make this request either directly to the NMDP/CIBMTR or through his or her corresponding Transplant or Donor Center. If the subject's sample has already been given to an investigator at the time he/she asked to withdraw from the Research Repository, the investigator will be instructed to remove the subject's sample from the study set.

10. Confidentiality

10.1 Coded Sample Inventory and Links to Personal Identifiers

All records pertaining to the identity of participants in the NMDP Research Repository will be kept private and confidential. Personal identifying information will only be released with the express written permission of the participant.

Blood samples and all records associated with blood samples will be labeled only with a numeric code that contains no personal identifiers. A link does exist between the participant's name and the numeric code. This link is not available to staff at the NMDP Research Sample Repository. The link will never be released to an investigator.

10.2 Reporting Requirements for Research Sample Requests

Progress reports on the status of research using samples obtained from the NMDP Research Repository must be submitted as required by the NMDP/CIBMTR.