CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH®

PROTOCOL FOR A RESEARCH DATABASE

FOR

HEMATOPOIETIC CELL TRANSPLANTATION, OTHER CELLULAR THERAPIES AND MARROW TOXIC INJURIES

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January 2017
Version 7.5

ClinicalTrials.gov Identifier: NCT01166009

NMDP IRB Approved 02/08/2017 through 07/29/2017
IRB-2002-0063, Research Database Protocol, Version 7.5

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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 cell (HC) donors. Physicians search the NMDP Registry on behalf of patients in need of an HC 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 HC transplant.

In addition, the Federal contract also recognized that the NMDP could play a critical role in responding to contingency events; primarily radiation and chemical exposures occurring either accidentally or resulting from military or terrorist actions that cause a marrow toxic injury.

1.2. Center for International Blood and Marrow Transplant Research®

The International Bone Marrow Transplant Registry (IBMTR), located within the Department of Medicine of the Medical College of Wisconsin, was established in 1972 to monitor and study outcomes of bone marrow transplants. In 2004 the NMDP and IBMTR established the Center for Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is an affiliation between the NMDP and the Medical College of Wisconsin. The CIBMTR has both a Minneapolis campus located within the NMDP offices and a Milwaukee campus at the Medical College of Wisconsin. The NMDP Research Program is accomplished through the CIBMTR.

The CIBMTR has a network of more than 500 centers worldwide that contribute detailed research data on consecutive allogeneic related and unrelated and autologous hematopoietic cell transplants. In addition, NMDP centers responsible for managing unrelated donors contribute detailed data on the donation and recovery of unrelated donors. In 2011 CIBMTR activities were expanded to include uses of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection.

The CIBMTR Research Database is comprised of databases maintained at the NMDP and the CIBMTR Milwaukee campus.

1.3. Establishment and Purpose of the Research Database

The primary goal of the CIBMTR Research Program is to improve the safety and effectiveness of hematopoietic cell (HC) transplantation for both donors and recipients. The NMDP database was established in 1989 and the IBMTR database was established in 1972. The Research Database contains demographic and clinical data on allogeneic related and unrelated donor and autologous HC transplants. Data are also collected on unrelated donors and their donation experiences. The data contained in the research databases are observational data. CIBMTR does not

determine which therapies are used for patients, but rather collects information regarding therapies as they are applied by transplant centers.

Secondary goals of the CIBMTR Research Program are to understand uses of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection, and to improve treatments and outcomes for those individuals who have been exposed to radiation or other chemicals that are toxic to marrow. In these cases, exposure data, organ injury data, treatment data, and outcomes data are collected.

The NMDP and the CIBMTR are the sole custodians of the data in the Research Database. The NMDP and the CIBMTR are responsible for determining who has access to the data in the Research Database (see Section 6 "Studies Involving Data in the Research Database"). The NMDP and CIBMTR are responsible for determining if and when data will be removed from the database or shared with others.

The primary purpose of the Research Database is to have a comprehensive source of observational data that can be used to study HC transplantation. A secondary purpose of the database is to have a comprehensive source of data to study marrow toxic injuries and the application of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection. Researchers whose study proposals are reviewed and approved in advance by the CIBMTR may use data for studies examining HC transplantation and its effects on recipients and donors, to study marrow toxic injury, or to study regenerative medicine or immune-based therapy, including for malignancy or infection. The following are types of studies in which these data may be included. Studies to determine:

- How well recipients recover from their transplants or cellular therapy;
- How recovery after transplantation or cellular therapy can be improved;
- Long-term outcomes after transplantation or cellular therapy,
- How access to transplantation or cellular therapy for different groups of patients can be improved, including studies designed to inform insurance/government payer policy, such as U.S. Medicare policy;
- How well donors recover from collection procedures;
- Success of different treatment models for marrow toxic injury;
- The long-term effects of exposure to radiation or other chemicals;
- The application and success of transplantation in the management of marrow toxic injuries;
- The application and success of hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection

Certain studies may require that data in addition to what already exists in the Research Database be collected in order to answer the research question. This protocol makes provisions for additional data collection from existing medical records (see Section 4.4 "Study Specific Data"). Section 6, "Studies Involving Data in the Research Database", describes the process for releasing data to investigators.

2. Eligibility to Participate in the Research Database

2.1. Recipient Eligibility Criteria

Any recipient of an unrelated or related donor or autologous HC transplant (includes cells collected from peripheral blood, bone marrow or cord blood) or any recipient of cellular therapy in a CIBMTR center is eligible to participate in the Research Database. This includes adults with and without decision making capacity, and children.

2.2. Individual with Marrow Toxic Injury Eligibility Criteria

In the event of a radiation exposure accident, the NMDP has a radiation injury treatment network, whose purpose is to collect data to understand the outcomes of patients treated under these circumstances. Any individual who is treated for a marrow toxic injury at a center participating in the NMDP's Radiation Injury Treatment Network (RITN) is eligible to participate in the Research Database. This includes adults with and without decision making capacity, and children. Eligible individuals may have received supportive care only, growth factor support, HC 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.

2.3. Unrelated Donor Eligibility Criteria

All donors registered on the NMDP Registry who have been requested to donate a product for a recipient are eligible to participate in the Research Database.

2.4. Informed Consent

All U.S. participants will be provided information about participation in the Research Database and must sign an Institutional Review Board (IRB) approved informed consent document indicating their consent to participate in the database. Whenever possible, patients should be informed about the protocol and asked to provide consent to participate prior to the transplant. In the rare circumstance where that is not possible, it is acceptable to obtain the patient's consent after the transplant has occurred. Documentation of assent and of parent or 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. To confirm that participants have given consent to participate in the Research Database, the first form submitted on a participant includes confirmation that the participant signed the informed consent document.

Non-U.S. centers contributing data to the Research Database will provide written assurance that the submission of data to the CIBMTR Research Database has on-going oversight by their local Ethics Review Board/Medical Ethics Committee and all national regulations are followed.

2.4.1. Minor Assent

The NMDP Research Database includes pediatric recipients. The procedural risk involved in this protocol meets the definition of minimal risk set forth in 45 CFR 46.102 (i) "*Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."* Participation on this protocol requires submission of medical data from recipients that are available directly from the participant's medical record.

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 45 CFR 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/legal guardian 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.

3. IRB Approval Process for Research Database

All U.S. centers must have an IRB-approved protocol and consent forms prior to submitting data about transplant recipients, transplant donors, or individuals with marrow toxic injury, to the Research Database. The center's designated IRB may not waive informed consent requirements under this protocol. Recipients, individuals with marrow toxic injury and donors must provide informed consent for submission of data to the Research Database.

Local IRB review and approval is necessary except in the case of centers that list the NMDP IRB as a designated IRB on their Federal Wide Assurance (FWA) and have an IRB Authorization Agreement in place with the NMDP that includes the Research Database protocol. This protocol and its associated consent forms are provided to centers. Centers are required to submit this protocol and consent forms to their designated IRBs for review and approval.

International centers must follow their own national regulations and provide assurance to the CIBMTR that national regulations are being followed.

3.1. IRB Approval Process

- The 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 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 data for research purposes as soon as the site's Principal Investigator receives 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 data for research purposes until IRB-approval has been obtained.
- In cases where the center has designated the NMDP IRB on their center's FWA, and an IRB Authorization Agreement is in place for the Research Database protocol, the center does not need to obtain any additional IRB approval.

4. Collection of Data

4.1. Collection of Recipient Data

Recipient data are collected from pre-existing data within the recipient's medical record chart at the transplant center. Transplant Centers complete the forms at the following time-points.

Time-point	Data Collected
At registration	Name Social Security Number (U.S. participants only) Mother's maiden name City State Country of birth
At the time of transplant	Demographic data such as race and ethnicity, gender, birth date, Median household income (U.S. participants only), Education (U.S. participants only), occupation HLA typing data Pre-transplant disease-specific data such as blood counts, disease status, cytogenetics Co-existing disease at the time of transplant

	Functional status Organ function prior to transplant History of infection exposure prior to transplant Conditioning regimen HSC product manipulation
100 days, six months, one year, two year, post-transplant	Engraftment – neutrophil and platelet recovery Acute and chronic GVHD Chimerism Organ function New malignancy Disease Status Functional status Ability to return to work or school Second transplant Donor leukocyte infusion
Annually starting year three	Acute and chronic GVHD New malignancy Disease Status Functional status Ability to return to work or school Second transplant
At time of death	Primary and contributing cause of death

4.2. Collection of Marrow Toxic Injury Data

Data from individuals with marrow toxic injury are collected from pre-existing data within the individual's medical record chart at the transplant center. Transplant Centers complete the forms at the following time-points.

Time-point	Data Collected
At registration	Name Social Security Number (U.S. participants only) Mother's maiden name City State Country of birth
At the time of initial evaluation	Demographic data such as race and ethnicity, gender, birth date, Pre-existing medical problems Exposure history Blood counts and marrow status Treatment data
At follow-up time points	Response to treatment including: Blood counts

	Laboratory and clinical data pertaining to organ injury New malignancy Functional status Additional treatments Other complications following the marrow toxic injury
At time of death	Primary and contributing cause of death

4.3 Collection of Unrelated Donor Data

Unrelated donor data are collected at the time a donor joins the Registry, when a donor is requested for confirmatory typing to determine if he/she is a match with a potential recipient, during the work-up phase to determine eligibility to donate HC, and post-collection of the HC product. Donor Center staff, and in some cases Transplant Center staff (i.e., confirmatory HLA typing data), complete the forms at the following time-points and submit them to the NMDP. All data submitted are abstracted from the donor's donation record maintained at the Donor Center, the Apheresis Center or marrow Collection Center. All data are collected as part of the standard donation process.

Additionally, donor cells may be tested to determine the number and types of cells, and to test for sterility and other factors important to the transplant. Data collected during these tests may also be used for research purposes.

Time-point	Data Collected
At the time the donor joins the Registry*	HLA typing Race Gender Date of birth
At the time a donor is requested for confirmatory typing*	HLA typing (submitted by transplant center) Infectious disease markers for hepatitis B and C, syphilis, HIV, CMV, HTLV I/II Weight ABO, Rh (D^U) type Allogeneic blood transfusion Number of pregnancies
At the time of the donor work-up for HC donation	Pre-existing medical conditions Infectious disease markers for hepatitis B and C, syphilis, HIV, CMV, HTLV I/II ABO, Rh (D^U) type Serum pregnancy test Screening for hemoglobin S (sickle hemoglobin)
During filgrastim injections (PBSC donors only)	Complete Blood Count Modified Toxicity Criteria
At the time of product collection*	Number and type of cells Sterility

	Other product factors related to transplant
Post HC collection Weekly until recovery One month, six month post collection Annually	Adverse events related to HC collection Ability to return to work, school, and leisure activities Complete Blood Count (at annual follow-up only) Modified Toxicity Criteria Health status

* These data are collected as part of the search and donation process and will only be included in anonymous research studies or studies that are deemed non-human subject research by the criteria included in the October 2008 OHRP Guidance titled *Research Involving Coded Private Information or Biological Specimens*, unless the donor gives consent to participate in the Research Database at the time he/she is requested to donate for a recipient. If consent is given, these data could be used in a linked research study.

4.4 Collection of Study Specific Data

In addition to the standard data collected at specified time points from recipients and donors (see Section 4.1 "Recipient Data", 4.2 "Marrow Toxic Injury Data" and Section 4.3 "Donor Data"), additional participant data may be collected as needed for a specific study. In these cases, any of the required additional data would be data that are available in the participant's medical records. Examples of additional data that may be requested for a specific study are more detailed clinical data at time of diagnosis or more detailed disease status data post-transplant. In no cases would the recipient, individual with a marrow toxic injury or donor be contacted in order to obtain additional data.

5. Collaboration with Other Registries

The CIBMTR has established collaborative relationships with the European Group for Blood and Marrow Transplant (EBMT) and EuroCord.

The EBMT, a non-profit organization based in Maastricht, The Netherlands, was established in 1974 and maintains a research database on outcomes of allogeneic and autologous transplants performed at its member centers. Like the CIBMTR, the EBMT is committed to improving the safety and efficacy of HC transplantation for both donors and recipients. To facilitate international research efforts in HC transplantation, the EBMT routinely provides data on HC transplants reported to the EBMT to the CIBMTR. Data provided by the EBMT does not include any individually identifiable data beyond birth date, location of transplant, treatment, relapse and death dates.

To evaluate cord blood transplants, the EBMT organized EuroCord, a separate European registry of cord blood recipients. The CIBMTR has an agreement with EuroCord to exchange outcomes data. The CIBMTR will provide outcomes data to EuroCord on any U.S. recipient who received a cord blood unit from a non-U.S.

NetCord cord blood bank, and EuroCord will send outcomes data to the CIBMTR on any recipient who received a cord blood unit from a U.S. cord blood bank at a non-U.S. EuroCord participating institution.

CIBMTR will share data with the United States Immunodeficiency Network (USIDNET) for inclusion in the USIDNET database for use in future research as determined by USIDNET. Only data from recipients who are enrolled in both the USIDNET database protocol and the CIBMTR Research Database protocol will be exchanged with USIDNET.

The CIBMTR may also engage in discrete studies with other registries where data from subjects in both registries will be combined for analysis. In these cases subject identifiers will be exchanged with the other registry to ensure that the cases in each registry are properly linked. An example of this type of registry is the End Stage Renal Disease (ESRD) Network. Any study that will use identifiers to match subjects in another registry with subjects in the CIBMTR Research Database will require administrative approval by the NMDP IRB Chair or designated NMDP IRB member.

6. Studies Involving Data in the Research Database

6.1. Who May Request Access to Data

The data in the Research Database are available to researchers both within the CIBMTR network and outside the network. The CIBMTR defines the policies and procedures for release of data.

6.2. How Requests Are Reviewed/Approved

Any legitimate investigator may propose observational research studies to the CIBMTR. Research Database proposals are reviewed and approved by one of the CIBMTR's scientific committees to ensure that the study is scientifically sound. If the study is scientifically sound, the NMDP IRB Chair will perform an administrative review of the study protocol to ensure that it is within the limits defined in the Research Database protocol and is covered by the participant's informed consent document for the Research Database. Studies that fall outside the limits defined the Research Database Protocol will be reviewed by the NMDP IRB. In these cases, additional consent may be required from the participant. Once the study has been approved, the NMDP and the MCW IRB are informed of new studies that are added to the overall research portfolio. A data extract plan is prepared and the data necessary to conduct the study are extracted from the Research Database into a study-specific research dataset. The data extract never includes individually identifiable data beyond treatment center and treatment, relapse and death dates.

In most cases the data analysis for a study is conducted by NMDP and CIBMTR research staff in Milwaukee or Minneapolis. Data from these analyses are shared with investigators, but always as summarized, aggregate data. On the rare occasion

where analysis will occur at an individual investigator's institution, no identifying information is released beyond a randomly generated ID number (distinct from the CIBMTR ID numbers) where CIBMTR maintains the code for the random ID number. At no time is an individual investigator given the names of participants, or the identity of the center where the participant was treated. All relevant dates pertaining to a study are replaced with calculated time interval values.

6.3 Studies Designed to Inform U.S. Medicare Policy

The United States Centers for Medicare & Medicaid Services (CMS) provides expanded payment coverage for some HCT indications under Coverage with Evidence Development (CED). To qualify for coverage, transplants for these indications must take place within a CMS-approved clinical study that meets federal guidelines. CIBMTR develops prospective observational clinical studies for HCT indications under CED and submits to CMS for approval. These prospective observational studies rely only on data collected under the Research Database Protocol. Patients enrolled on CIBMTR studies for indications under CED will sign a separate consent form under the Research Database Protocol for participation in a CMS CED-approved study. These patients will be invited to participate in both the CMS CED study and the Research Database protocol. Patient participation in the CMS CED study is not dependent on their participation in the Research Database Protocol.

7. Participant Withdrawal from the Research Database

At any time a participant may request that his or her data no longer be made available for research purposes. The participant may make this request either directly to the NMDP or CIBMTR or through his or her corresponding center.

8. Data Confidentiality

Access to all information in the Research Database is tightly controlled with passwords and logins at multiple levels. Access to the Research Database is limited to those employees who have specific job responsibilities related to the database.

All paper forms containing participant information are filed in a locked area. Only those employees who have specific job responsibilities related to the files have access to the files.

Donors are assigned a donor identification (DID) number when they join the NMDP Registry. The DID contains no identifying information. This DID is used to track all donor information in the Research Database.

Recipients of transplant or hematopoietic cells for regenerative medicine or immune-based therapy, including for malignancy or infection, and individuals with marrow toxic injury are assigned a unique identification number when the treatment center registers them with the Research Database. Participant first and last name, social security number (US participants only), mother's maiden name, and city,

state and country are collected at the time the unique identification number is assigned to ensure that the participant has not been previously registered by another center. These identifying data are stored in a secure database that is totally separated from the Research Database. These identifying data are never included in data sets for analysis. The unique identification number contains no identifying information within it. This number is used to track all information about the participant in the Research Database.

The identity of participants in the Research Database is kept confidential at all times. Identifying information that is kept in the Research Database for recipients includes transplant date, birth date, and location of transplant. Identifying information that is kept in the research database for individuals with marrow toxic injury includes, exposure date, birth date, location of treatment. Identifying information that is kept in the research database for donors is birth date, donor center, and date and location of HC collection. Data released to investigators outside the CIBMTR does not include identifying data such as birth date and location of treatment.

All research staff at the CIBMTR and the NMDP maintains up-to-date training in protection of human subjects. This training is received through the Collaborative IRB Training Initiative (CITI) program. This is a web-based training program offered through the University of Miami.

Additionally, systems and applications within the NMDP are certified by the Health Resources Services Administration Office of Information and Technology.