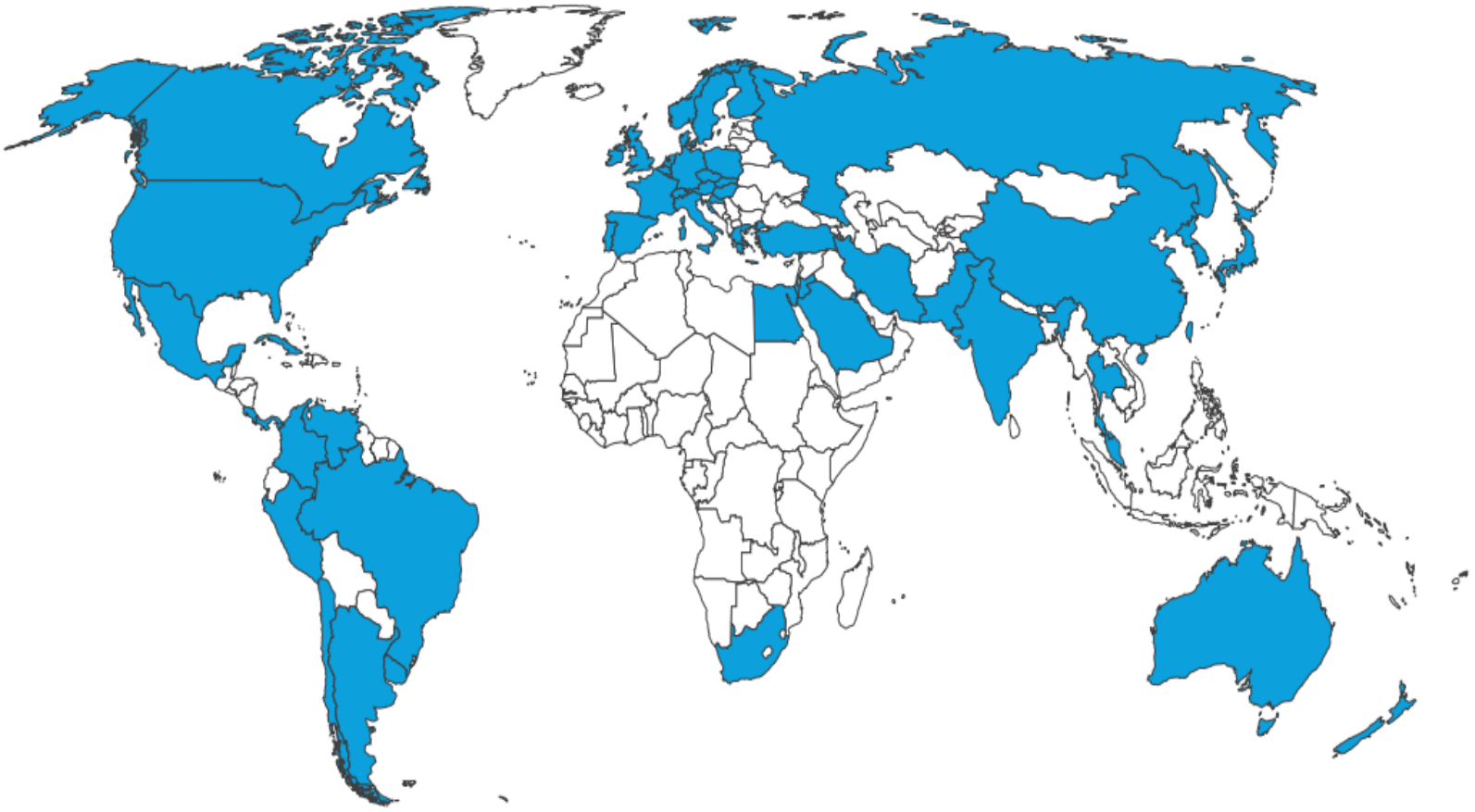
CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Sharing Knowledge.
Sharing Hope.

Manual of Operations

Version 6.1



CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program®/Be The Match® and Medical College of Wisconsin

TABLE OF CONTENTS

WEB LINKS

Throughout this report, electronic links to webpages and documents are provided; they are underlined and italicized for identification. If you are unable to access items using the links provided, enter the underlined and italicized words into a general search engine or the search engine at the top of the CIBMTR website (cibmtr.org).

CHAPTER 1: ORGANIZATION

1.1 MISSION

The Center for International Blood and Marrow Transplant Research (CIBMTR) promotes collaborative research to understand and improve access to and outcomes of cellular therapies for the people we serve. A research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW), the CIBMTR facilitates critical research through medical, scientific, and statistical expertise; a large network of participating centers, a unique and extensive clinical database; and a robust and comprehensive biospecimen repository.

1.2 HISTORY

In July 2004, the CIBMTR was formed through an affiliation of the International Bone Marrow Transplant Registry (IBMTR) / Autologous Blood and Marrow Transplant Registry (ABMTR) of MCW and NMDP, now known as NMDP/Be The Match. The purpose of the affiliation was to establish a formal working relationship for collaborative research to advance the field of hematopoietic stem cell transplantation (HCT) and related research areas, including cellular therapies. In 2004, the IBMTR / ABMTR (MCW) and NMDP agreed to conduct all HCT-related research activities jointly, and a Joint Affiliation Board maintains high level oversight (**Figure 1.1**). The CIBMTR continues to integrate with NMDP/Be The Match and MCW at many levels; this document includes references to the support provided by both parent organizations' Human Resources, Legal, Information Technology (IT), and Finance Departments.

Prior to the affiliation, the IBMTR / ABMTR and NMDP had broad research expertise in HCT, including observational research and clinical trials. The IBMTR began in 1972 as a voluntary organization of 12 transplant centers involving 50 transplant patients worldwide. In 1989, the IBMTR began collaborating with the ABMTR in its research efforts. By 1994, more than 400 institutions in more than 40 countries were involved in sharing patient data and conducting scientific studies with the IBMTR / ABMTR (MCW). The NMDP was established in 1987 to provide unrelated donors for patients in need of HCT. The NMDP also conducted outcomes research and developed a Research Sample Repository of donor-recipient samples. At the time of the affiliation, the NMDP network included 164 transplant centers, 80 donor centers, 101 collection centers, 89 apheresis centers, and 17 cord blood banks. The CIBMTR was formed in an effort to unite the research efforts and complementary strengths of both organizations.

IBMTR / ABMTR strengths included:

- A strong record of clinical research, including publications in HCT and statistical methodology;
- A long history of effective collaborations with a large network of international centers;
- Key personnel with acknowledged leadership in the field and combined training in both clinical HCT and biostatistics;
- An extensive database of clinical information on autologous as well as related and unrelated donor allogeneic transplant recipients.

NMDP strengths included:

- Experience with a large network of donor, collection, and transplant centers;

- A database that included almost all unrelated donor transplants in the United States (US) with donor-recipient biorepository samples for a large subset of these transplants;
- A business office experienced in contractual relationships with biorepository samples, contract laboratories, pharmacies, and other organizations essential for trial-related activities;
- A patient advocacy office experienced in providing educational materials for patients treated in or considering participation in clinical trials and in conveying information derived from CIBMTR studies.

In 2005, the US Congress passed legislation to establish the C.W. Bill Young Cell Transplantation Program, a component of which is the Stem Cell Therapeutic Outcomes Database (SCTOD) (**Chapter 6**). The purpose of the SCTOD is to increase the availability, safety, and efficacy of allogeneic HCTs and to collect data on all allogeneic HCTs done in the US as well as all HCTs done outside the US using products procured through the Program. The CIBMTR was awarded the contract to operate the SCTOD in 2006. As a result, the CIBMTR was established as the national registry to which data on all allogeneic transplants performed in the US must be reported. This manual includes a description of the changes that were made to successfully execute the requirements of the contract.

The CIBMTR Research Database has been used to demonstrate safety and efficacy of diverse HCT approaches, optimize selection of donor and graft sources, evaluate new drugs and strategies to increase efficacy and prevent complications, assess center-specific outcomes, and predict patient outcomes based on clinical and treatment characteristics. Based on this successful model, in 2014 the CIBMTR adapted its infrastructure to meet the need to assess the real-world safety and efficacy of non-HCT cellular therapy.

1.3 OVERVIEW

The CIBMTR collaborates with the global scientific community to advance HCT and cellular therapy research worldwide. It facilitates research with important effects on clinical practice. This prospective and observational research is accomplished through medical, scientific, and statistical expertise; a large network of centers, a comprehensive biospecimen repository, and a Research Database containing clinical data for more than 500,000 patients.

The CIBMTR network includes scientists from approximately 420 centers worldwide. Most centers report patient outcomes data electronically through FormsNet^{SM}, the CIBMTR's web-based application. Centers are also able to report data through paper data collection forms if they are unable to access the electronic system. The CIBMTR Research Database is a large repository of information on patients who have been treated with allogeneic or autologous transplantation or procedures in which hematopoietic stem cells were used for clinical applications other than HCT as well as with cellular therapies and regenerative medicine. In addition to maintaining this Research Database, the CIBMTR provides expert statistical support to investigators analyzing these data. The data and the analytic support available through the CIBMTR Coordinating Center have contributed to the successful completion of more than 1,400 publications.

1.3.1 Programs

The CIBMTR has six major research programs:

- **Statistical Methodology Research Program (Chapter 5):** This program facilitates development of new statistical approaches to HCT and cellular therapy research, prepares educational review articles on data analysis, and provides input to other scientific projects. The Chief Statistical Director serves as head of this program, a unique asset of which is the expertise of partner PhD-level Biostatisticians from the MCW Division of Biostatistics. A Statistical Director is assigned to advise each of the 15 CIBMTR Working Committees **(Chapter 2)** and oversees the work and participates in the training of the Master of Science (MS)-level Statisticians.
- **Clinical Outcomes Research Program (Chapter 6).** This program focuses on the effects of HCT and cellular therapy on recipients and donors as well as the clinical and treatment factors influencing the effectiveness of the therapy. These topics often cannot be addressed in single-center studies or randomized trials, and the Research Database is a key component of this research. The program includes research conducted within the Scientific Working Committees (**Section 6.1**) and SCTOD (**Section 6.2**) as well as research related to cellular therapy (**Section 6.3**), Medicare Coverage with Evidence Development studies (**Section 6.4**), and patient-reported outcomes (**Section 6.5**).**Immunobiology Research Program (Chapter 7).** This program facilitates studies using the Research Sample Repository. It provides unrelated and related (since December 2007) donor-recipient specimens from the Research Sample Repository linked with comprehensive CIBMTR clinical data to qualified investigators for genetic and immunologic studies. This program is overseen by the relevant Working Committee and the NMDP/Be The Match Histocompatibility Advisory Group.
- **Clinical Trials Support Program (Chapter 8).** This program, which facilitates clinical trials that focus on issues in HCT and cellular therapy, has two components:
    - **The Data and Coordinating Center (DCC) of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).** The DCC coordinates the activities of the BMT CTN, which was established in October 2001 to conduct large, multi-center clinical trials. DCC activities include overseeing the implementation and completion of clinical trials, facilitating effective communication and cooperation among participating centers and collaborators, and coordinating patient enrollment to trials nationwide. The DCC is overseen by the CIBMTR, NMDP/Be The Match, and The Emmes Company (a contract research organization).
    - **The Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT).** The RCI BMT, established as a formal program in 2006, provides support to investigators using CIBMTR data to design and conduct multi-center Phase I, II, and III trials. The RCI BMT has three major activities: Investigator Support Services, Survey Research, and Clinical Study Management. The CIBMTR Clinical Trials Advisory Committee oversees RCI BMT projects.
- **Health Services Research (HSR) Program (Chapter 9).** This program facilitates studies in a variety of focus areas, including economic and health-related cost analyses,

disparities in and barriers to access, treatment decision making and support, health care utilization, quality and value of care, and survey research. Its overall objectives are to increase access to HCT and cellular therapy and to improve patient outcomes by developing a well-balanced portfolio of health policy and services research and analyzing health services issues from a sociological perspective.

- **Bioinformatics Research Program (Chapter 10).** This program analyzes genetic data, particularly the major histocompatibility complex (MHC) gene family. Research activities include improving the match algorithm and data standards as well as conducting registry modeling.

CIBMTR research activities are supported by several sources, including:

- U24 cooperative agreement jointly funded by the National Cancer Institute (NCI) (lead institute); National Heart, Lung, and Blood Institute (NHLBI); and National Institute for Allergy and Infectious Diseases (NIAID);
- U24 cooperative agreement jointly funded by NHLBI (lead institute) and NCI;
- U24 cooperative agreement funded by NCI (lead institute) and the National Institute on Minority Health and Health Disparities;
- Contract from the Health Resources and Services Administration (HRSA).

Additional support is provided by NMDP/Be The Match, MCW, foundations, and corporate organizations. See **Chapters 17** and **18** for more information.

1.3.2 Sources and Uses of Data

The CIBMTR represents an international group of centers that provide data on consecutive transplants and some uses of cellular therapy to its bi-campus Coordinating Center. The CIBMTR performs and supports studies using these data, in some cases linking the data to research samples in the Research Sample Repository. Researchers can propose studies to, or request data from, the CIBMTR for their own investigations.

HCT data is collected at two levels using data collection forms developed by the CIBMTR, the Transplant Essential Data (TED) form-level, and the Comprehensive Report Form (CRF)-level. The TED forms include internationally accepted standard data fields focusing on critical HCT variables. CRFs capture extensive patient, disease, treatment, and outcome data for a subset of patients. Cellular therapy data is collected using the CTED (Cellular Therapy Essential Data) suite of forms. For more information about data collection processes, see **Chapter 11** and the *Data Management* webpage.

Requests for CIBMTR data must adhere to the CIBMTR rules for releasing data (**Chapter 13**). Investigators requesting CIBMTR data must follow appropriate procedures for:

- Submission of proposals (**Chapter 6**);
- Investigator engagement in developing and completing research studies (**Chapter 6**);
- Rules of authorship (**Chapter 3**);
- Submission of data (**Chapter 11**).

Data can also be requested through the *Bone Marrow and Cord Blood Donation and Transplantation* website.

1.4 ORGANIZATIONAL STRUCTURE

The CIBMTR represents a large network of approximately 420 centers that submit data for patients. The CIBMTR Coordinating Center is staffed by approximately 210 employees who work within its functional areas:

- Statistical Operations;
- Bioinformatics Operations;
- Immunobiology Operations;
- Clinical Trials Operations;
- Data Operations;
- Business Development;
- Business Operations;
- Information Technology;
- Human Research Protection;
- Quality Assurance;
- Finance and Administration Milwaukee.

The Executive Director provides general oversight of the organization and reports directly to the Joint Affiliation Committee, comprised of members from both NMDP/Be The Match and MCW. The Chief Scientific Director is responsible for administrative and scientific operations. The Chief Statistical Director is responsible for the oversight of statistical methodologies. The CIBMTR committee governance structure (**Chapter 2**) ensures the organization meets the needs and priorities of its medical and scientific communities. The scientific program structure of the CIBMTR is shown in **Figure 1.1**, which represents the CIBMTR's basic program components and defines the leadership. The Vice Presidents for Research Operations in Milwaukee and Minneapolis are responsible for the oversite of CIBMTR operational teams. The operations organizational structure is provided in **Figure 1.2** and outlines the integration of scientific oversight within key operational areas.

Figure 1.1: CIBMTR Scientific Organizational Structure

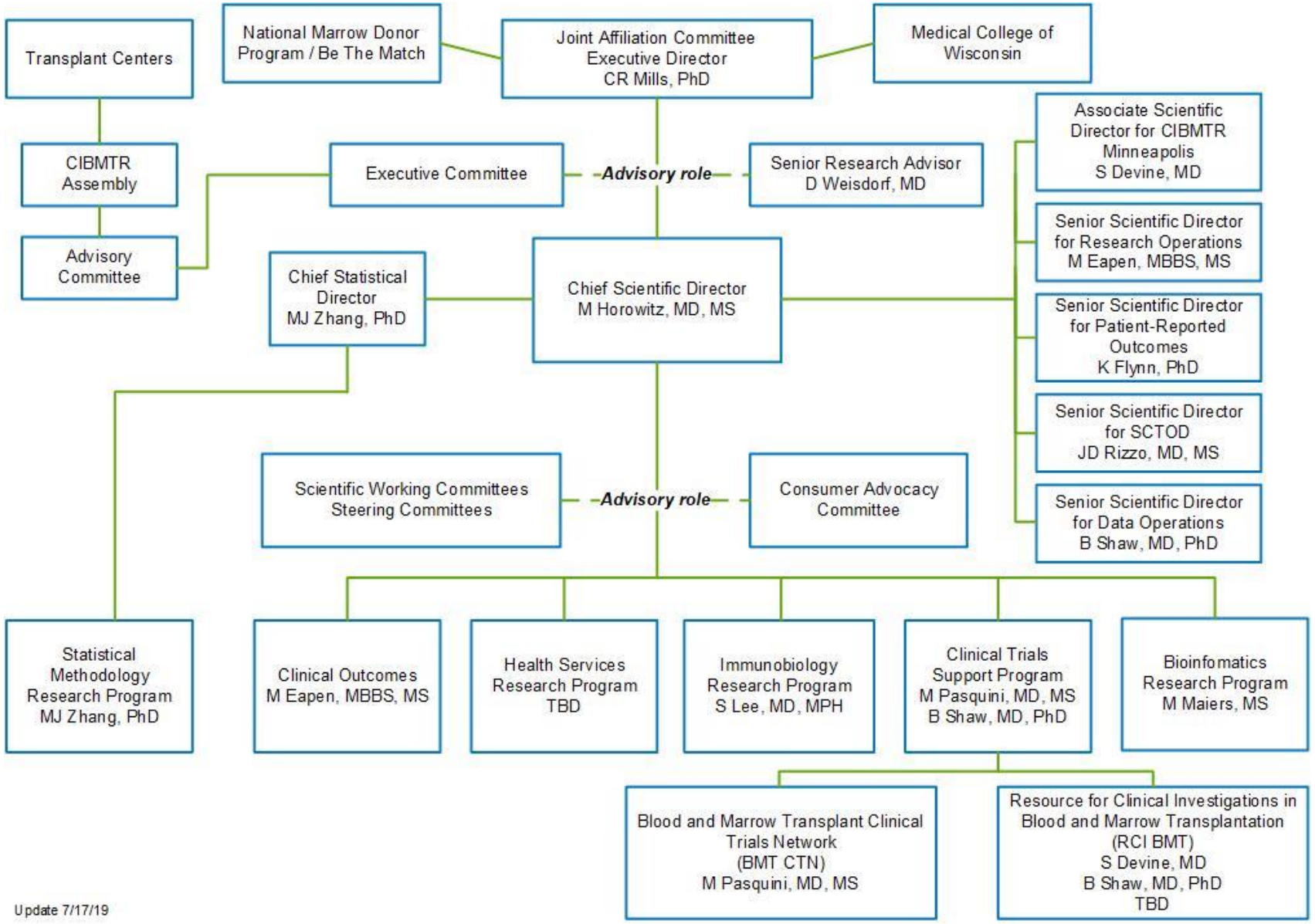


Figure 1.2: CIBMTR Operations Organizational Structure with Scientific Oversight

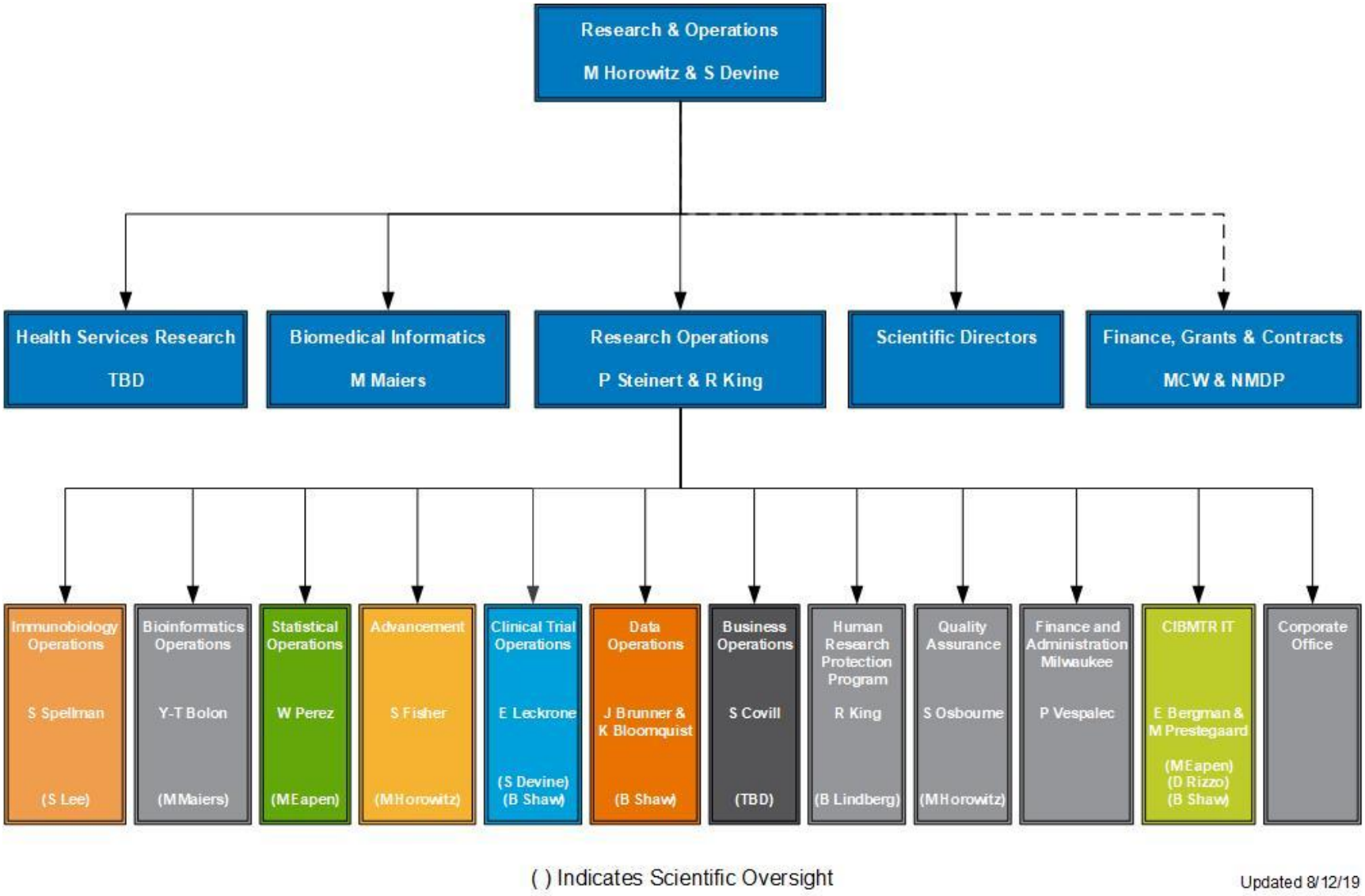


Figure 1.2.1: CIBMTR Operations Organizational Structure Details (Page 1)

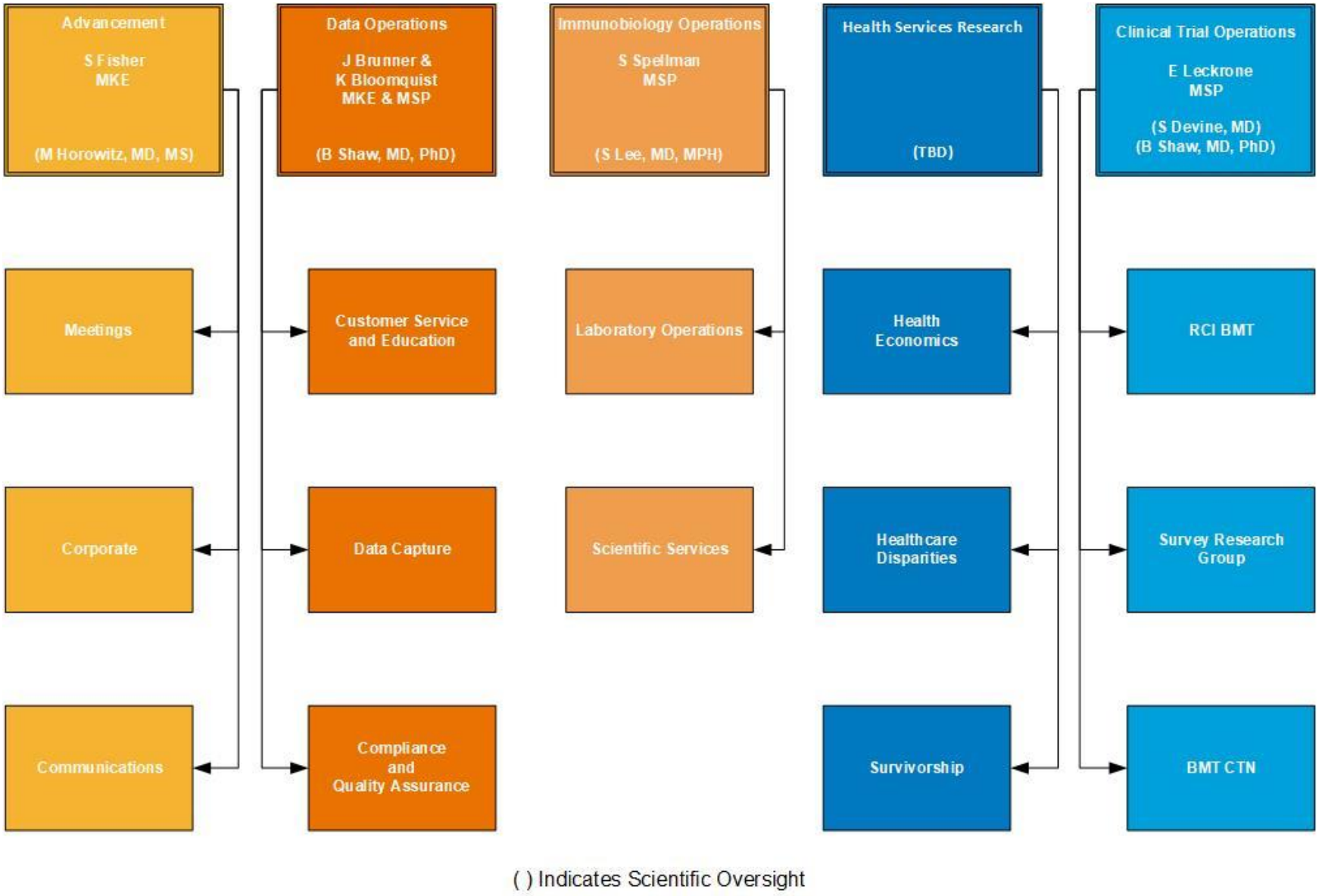
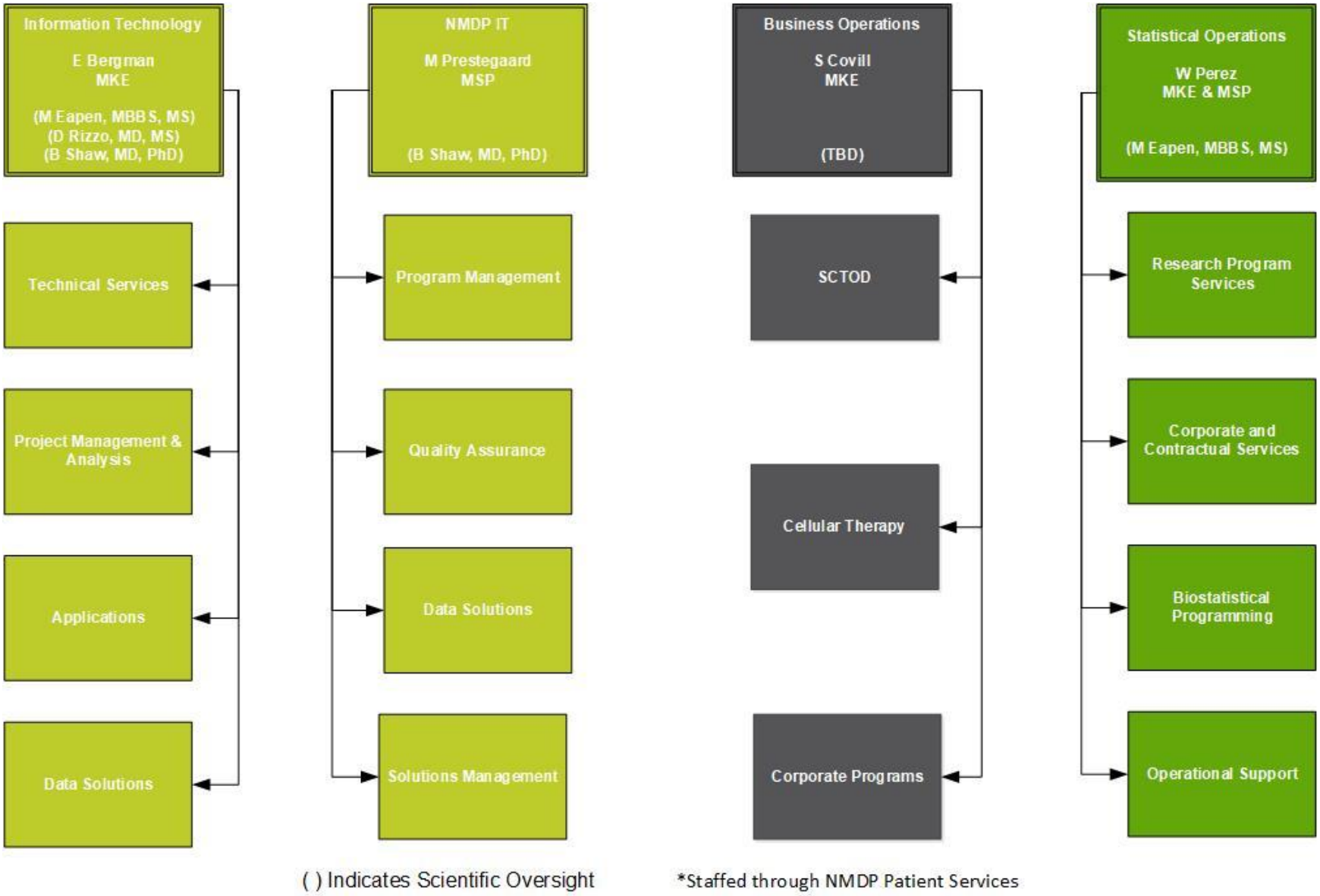


Figure 1.2.2: CIBMTR Operations Organizational Structure Details (Page 2)



CHAPTER 2: COMMITTEE STRUCTURE

The CIBMTR committee structure is designed to elicit broad input from the HCT and cellular therapy community. It ensures the activities of the organization and its use of resources are consistent with the priorities of this community. CIBMTR committees include experts in various disciplines and related diseases. Committees may also include representatives of CIBMTR's federal funding agencies, including the National Institutes of Health (NIH) and HRSA, as well as patient advocates.

All elected committee members and Working Committee Chairs must be from participating centers that submit CRF data and, for US centers, meet continuous process improvement (CPI) requirements (**Chapter 11**). Eligible individuals from non-US centers will show evidence of commitment to the CIBMTR mission through adequate reporting over the prior three years, regular attendance at the Transplantation and Cellular Therapy (TCT) Meetings of the American Society for Transplantation and Cellular Therapy (ASTCT) and CIBMTR (formerly known as the BMT Tandem Meetings), active membership in CIBMTR committees, and / or authorship on CIBMTR publications. The Nominating Committee may also consider putting forward candidates to represent other international registries. All committees, except the Joint Affiliation Board, have staggered terms of succession to preserve continuity. With the exception of the Consumer Advocacy Committee, administrative support for committee activities is provided by the CIBMTR Coordinating Center. Committee membership is evaluated periodically to ensure adequate representation. The overall CIBMTR organizational structure, including its committees, is shown in **Figure 1.1**.

2.1 CIBMTR ASSEMBLY

The Assembly is the voting membership of the CIBMTR. It includes one representative from each center that submits CRF data and meets CPI requirements (**Chapter 11**). The Assembly meets annually during the TCT Meetings. Assembly members receive periodic summaries of CIBMTR activities and elect members of the CIBMTR Advisory, Nominating, and Clinical Trials Advisory Committees.

2.2 ADMINISTRATIVE COMMITTEES

2.2.1 Joint Affiliation Board

As noted in **Chapter 1**, the CIBMTR was formed through an affiliation of the IBMTR / ABMTR at MCW and NMDP/Be The Match. A Joint Affiliation Board, with representation from both organizations, was established for general oversight of the CIBMTR budget and operations. The Joint Affiliation Board:

- Reviews and approves an annual budget;
- Periodically reviews and approves a research plan;
- Annually assesses CIBMTR productivity;
- Establishes other CIBMTR committees, as needed;
- Amends, as necessary, terms of the affiliation agreement;
- Reviews and approves data access and confidentiality policies.

Voting membership includes the NMDP/Be The Match Chief Executive Officer, NMDP/Be The Match Chief Financial Officer, and two MCW representatives appointed by the MCW Dean. One of the MCW representatives is assigned from the MCW Financial Controller's office. Non-voting

members are the CIBMTR Chief Scientific Director, Chief Statistical Director, Associate Scientific Director, Senior Scientific Director, and the CIBMTR Vice Presidents for Research Operations in Milwaukee and Minneapolis. The Board meets annually.

2.2.2 CIBMTR Advisory Committee

The Advisory Committee functions similar to a board of directors for the CIBMTR, providing oversight for CIBMTR policies and the scientific agenda, however, without fiduciary responsibilities. The major responsibility of this committee is to advise the operational leadership of the CIBMTR regarding scientific direction, policy, and priority use of resources. In this capacity, it is responsible for:

- Oversight and approval of the scientific agenda for the CIBMTR;
- Approval of policies for use of CIBMTR data;
- Approval of the Manual of Operations;
- Approval of Working Committee Chair appointments;
- Approval of elected individuals for positions on the Advisory, Executive, Nominating, Cellular Immunotherapy Data Resource (CIDR) Executive, and Clinical Trials Advisory Committees;
- Selection of the recipient of the Distinguished Service Award, which is presented annually at the TCT Meetings;
- Appointment of individuals to the Advisory Committee to provide:
    - Expertise in adult and pediatric clinical care;
    - Expertise in autologous, related donor, and unrelated donor transplantation and cellular therapy;
    - Expertise in donor selection, and graft collection and manipulation;
    - Representation of US and non-US centers;
    - Familiarity with CIBMTR operations;
    - Representation of patient, family, and donor interests;
    - Expertise in business, bioethics, and cord blood bank operations (as required by the SCTOD contract, discussed in **Chapter 6**).

Elected terms are three years and begin on March 1 following year-end elections. The exceptions are the shorter, one- and two-year terms of the Chair-Elect and Immediate Past Chair (see below). Elected individuals may serve multiple terms but not consecutively. Terms of appointed positions are also limited to three years but may serve one additional term if renewed by the Advisory Committee. Terms of ex officio voting members are indefinite based on indicated position in the organization.

Members elected by the Assembly include:

- Chair* (1): Three-year term;
- Chair-Elect* (1): One-year term prior to serving as Chair;
- Immediate Past Chair* (1): Two-year term after serving as Chair;
- Regional Vice Chairs: North America (1); Central / South America (1); Europe (1); Asia / Africa / Australia (1);
- At Large Members (12): From North America (6) and Non-North America (6).

Members appointed by the Advisory Committee include:

- ASTCT Representative (1);
- Business Expert (1);
- Bioethics Expert (1);
- Patient / Family Representatives (2);
- CIDR Representative (1);
- Cord Blood Bank Operations Expert (1).

Members appointed by the CIBMTR Executive Director include:

- Donor Center Representative (1);
- Collection Center Representative (1).

Ex officio voting members include:

- Be The Match / Navy Project Officer (1);
- MCW / NCI Project Officer (1);
- MCW / NHLBI Project Officers (2);
- MCW / NIAID Project Officer (1);
- Nominating Committee Chair *(chair will not vote on Nominating Committee tasks).*

Ex officio non-voting members include:

- Executive Director;
- Chief Scientific Director;
- Chief Statistical Director;
- Senior Scientific Director for SCTOD;
- Senior Vice President and Associate Scientific Director for CIBMTR Minneapolis;
- Executive Director CIBMTR Milwaukee;
- Vice President CIBMTR Minneapolis;
- Senior Manager of Data and Program Evaluation;
- Senior Research Advisor;
- MCW HRSA Project Officers or Representatives (2);
- NMDP HRSA Project Officer or Representative (1).

A call for nominations for elected positions occurs in spring for terms expiring the following spring. The Nominating Committee considers these nominations when preparing its slate of candidates and may make additional recommendations of their choosing. The slate is approved by the Advisory Committee and then distributed to the Assembly. Elections are held by electronic ballot in fall. As noted above, the CIBMTR Executive Director appoints the Collection Center and Donor Center Representatives. The current ASTCT President serves as the ASTCT representative, and the current CIDR Executive Committee Chair and Consumer Advocacy Committee Chairs serve as CIDR and Patient / Family Representatives, respectively. For all other appointments, the Nominating Committee identifies one or two eligible individuals and submits their name(s) for consideration to the Advisory Committee Chair. The Chair determines the final selection for the appointment.

In the event that a committee member relinquishes his / her position on the Advisory Committee prior to the end of the term and within the annual nomination cycle, replacement of that committee member follows the standard appointment or election process, and the committee member is elected to a three-year term. If a committee member relinquishes his / her position outside the annual nomination cycle, the position will remain open until it can be filled during the next nomination cycle.

Meetings of the Advisory Committee are held annually during the TCT Meetings. Additional meetings take place by conference call at least three times annually for review of the research agenda. Meetings are open to the public and to federal representatives, except during rare occasions when deliberations pose any confidentiality issues, such as discussions of individual center performance.

2.2.3 CIBMTR Executive Committee

The Executive Committee is a subcommittee of the Advisory Committee that provides ongoing advice and counsel to the CIBMTR Coordinating Center. The Executive Committee is responsible for ensuring that the organization carries out its mission and fulfills the requirements of CIBMTR policies and procedures. In this capacity, it:

- Provides direction to the Chief Scientific Director and Coordinating Center for scientific activities and policy decisions;
- Finalizes priorities for scientific studies after obtaining input from the Working Committees;
- Reviews results of audits and recommends measures to correct deficiencies;
- Appoints CIBMTR representatives, including a Program Chair, to the TCT Meetings Scientific Organizing Committee and selects the annual Mortimer M. Bortin lecturer.

This committee provides high level oversight to activities of the Working Committees and has the authority to remove and replace Working Committee Chairs who are not adequately fulfilling their roles or meeting organizational leadership expectations. The Executive Committee also handles policy violation issues as necessary.

The Executive Committee includes the Advisory Committee Chair, Chair-Elect or Immediate Past Chair, Regional Vice-Chairs, and the appointed members of the Advisory Committee (above). The CIBMTR Executive Director, Chief Scientific Director, Chief Statistical Director, Senior Scientific Director SCTOD, Senior Vice President and Associate Scientific Director CIBMTR Minneapolis, Executive Director CIBMTR Milwaukee, Vice President CIBMTR Minneapolis, Senior Manager of Data and Program Evaluation, Senior Research Advisor, Be The Match / MCW / HRSA Contracting Officer Representative, and MCW / HRSA Contracting Officer Representatives serve as non-voting ex officio members. Other ex officio members of the Advisory Committee (including the Be The Match / Navy Project Officer, MCW / NHLBI Project Officers, MCW / NIAID Project Officer, and Nominating Committee Chair) are not members of the Executive Committee but are invited to Executive Committee meetings and conference calls. The committee meets quarterly by teleconference.

2.2.4 CIDR Executive Committee

The CIDR Executive Committee is a subcommittee of the CIBMTR Advisory Committee that provides ongoing advice and counsel to the CIBMTR Coordinating Center relative to the Cellular Therapy Program. The CIDR Executive Committee is responsible for ensuring the organization carries out its mission and fulfills the requirements of CIDR initiatives, processes, and procedures. In this capacity, it provides oversight of:

- Forms development and revision;
- New and ongoing collaboration with centers;
- Input for selection of Scientific Working Committee Leadership;
- Coordination of activities with other Immuno-Oncology Transplantation Network (IOTN) programs;
- Policies for data sharing and increasing participation in CIDR activities;
- Priorities for CIDR scientific studies after obtaining input from the Working Committee;
- Compliance with the terms of the CIDR grant and progress toward its specific aims.

The committee provides high level oversight to activities of the Working Committees and has the authority to remove and replace Working Committee Chairs who are not adequately fulfilling their roles or meeting organizational leadership expectations. The CIDR Executive Committee also handles policy violation issues as necessary.

Members include:

- Chair (1): Three-year term;
- Members (5): Three-year term.

Ex-officio voting members include:

- CIBMTR Advisory Committee Chair (1): Three-year term;
- IOTN Steering Committee Chair (1);
- CIDR Project Officer (1).

Ex-officio non-voting members include:

- CIDR PI and CIBMTR Chief Scientific Director;
- CIDR Registry Director;
- CIDR Statistical Director;
- Senior Vice President and Associate Scientific Director CIBMTR Minneapolis;
- Executive Director CIBMTR Milwaukee;
- CIBMTR Senior Scientific Directors (2);
- CIBMTR IT Directors (2).

One member of the CIDR Executive Committee is asked to participate in the CIBMTR Nominating Committee to provide input and expertise for Working Committee and Executive Committee leadership selection.

2.2.5 CIBMTR Nominating Committee

The Nominating Committee is responsible for:

- Preparing a slate of candidates for new members of the Advisory, Executive, Nominating, CIDR Executive, and Clinical Trials Advisory Committees. Elections by the Assembly are held during the fall of each year for terms beginning on March 1 of the subsequent year.
- Making recommendations to the Advisory Committee for new Working Committee Chairs whose terms also expire February 28 of the next year.

The committee seeks input from the CIBMTR Assembly, Advisory Committee, and Working Committee Chairs to prepare the slate of Administrative Committee candidates and Working Committee Chair recommendations. The Coordinating Center distributes the mailed request for nominees. Nominating Committee deliberations follow by teleconference. The committee considers overall expertise and junior investigators interested in becoming more involved in CIBMTR activities as well as researchers from international centers. The list of incumbents is also taken into consideration to avoid single center over-representation, and, to the extent possible, the committee tries to identify suitable candidates with racial / ethnic and gender diversity. All nominees must provide conflict of interest disclosure prior to consideration.

The Nominating Committee includes six members, elected by the CIBMTR Assembly, to three-year terms. One member is selected based on specific expertise in cellular therapy research. In the event that a committee member relinquishes his / her position on the Nominating Committee before the end of the term and within the annual nomination cycle, replacement of the committee member follows the standard election process. If a committee member relinquishes his / her position outside the annual nomination cycle, the position remains open until it can be filled during the next scheduled nomination cycle. Due to the need to maintain staggered terms, the term of the new / replacement committee member is independently assessed. If possible, a full three-year term is offered. However, a shorter term may be offered to prevent the loss of multiple committee members at the same time. The term of this committee member then ends at the date of the original position, and the new member is eligible for nomination to a second term. The Nominating Committee Chair is recommended by the committee and approved by the Advisory Committee Chair. When appointed, the Chair will retain the role throughout the term of their committee membership. The Nominating Committee Chair also serves as the committee's representative on the Advisory Committee.

2.3 OTHER CIBMTR ADMINISTRATIVE COMMITTEES

Three other committees provide an additional level of administrative and scientific oversight in specific areas.

2.3.1 NMDP/Be The Match Histocompatibility Advisory Group

The NMDP/Be The Match Histocompatibility Advisory Group serves as the CIBMTR Immunobiology Steering Committee. It reviews and approves the use of donor-recipient specimens from the Research Sample Repository for CIBMTR studies. These studies link outcomes data with biologic and genetic factors derived from analyses of the biologic materials. The Advisory Group coordinates with the CIBMTR to develop, prioritize, and oversee

immunogenetics and histocompatibility research that utilizes the human leukocyte antigen (HLA) database and enhances performance of the CIBMTR and NMDP/Be The Match in their respective missions.

Membership is appointed by NMDP/Be The Match and includes national and international experts in the field and government representatives. Membership also always includes at least one CIBMTR Statistical Director and one CIBMTR Scientific Director. The committee is supported by knowledgeable CIBMTR and NMDP/Be The Match staff members who are closely associated with this unique and specialized activity. The Histocompatibility Advisory Group meets twice annually in person: At the TCT Meetings and in summer, usually in Minneapolis. It also meets by teleconference as needed.

2.3.2 Clinical Trials Advisory Committee

The primary function of the Clinical Trials Advisory Committee is to review and make recommendations regarding proposals submitted to the RCI BMT (**Chapter 8**), based on their scientific merit, feasibility, resource availability, and alignment with the CIBMTR's scientific agenda. It also advises the Clinical Trials Office on priority of proposed studies and reviews progress of ongoing studies. On occasion, the Clinical Trials Advisory Committee is asked to give input on protocols that are in development or on active protocols within the RCI BMT.

Ideas for studies come from within the CIBMTR and the external community. The proposal review process includes an initial evaluation by a Clinical Trials Office review team and further review by the appropriate CIBMTR Scientific Director and Working Committee Chair. The Clinical Trials Advisory Committee makes a final recommendation based on those reviews.

Members are elected by the Assembly for three-year terms. Terms may be extended if members hold Chair positions chosen from within the committee. Chairs are eligible to serve one additional two-year term with committee approval / recommendation. The Chair serves as a member of the committee for one year after their chair term ends. In the event that a committee member relinquishes his / her position on the Clinical Trials Advisory Committee before the end of the term and within the annual nomination cycle, a replacement will be determined through the standard appointment or election process, and the elected individual will hold a three-year term. If a committee member relinquishes his / her position outside the annual nomination cycle, the position will remain open until it can be filled during the next nomination cycle.

Elected members [a total of nine (includes chair), staggered to maintain continuity] include:

- Adult and pediatric transplant and cellular therapy physicians experienced in participating in clinical trials, trial design, and study conduct;
- Individuals experienced in representing donor interests (e.g., transfusion medicine);
- Non-physicians with experience in transplant recipient and donor issues.

Voting appointed members include the two Chairs of the Consumer Advocacy Committee.

Non-voting ex officio CIBMTR staff members include:

- Chief Scientific Director;
- Senior Research Advisor;
- Associate Scientific Director CIBMTR Minneapolis;

- Vice President CIBMTR Minneapolis;
- RCI BMT Scientific Directors (2);
- Senior Manager, Prospective Research;
- CIBMTR PhD Biostatisticians;
- NMDP/Be The Match Chief Financial Officer or designees;
- NMDP/Be The Match US Navy Project Officer.

The Clinical Trials Advisory Committee meets a minimum of once per year in person at the annual TCT Meetings and as needed throughout the year.

2.3.3 Consumer Advocacy Committee

The Consumer Advocacy Committee provides valuable patient and donor perspectives during the development of the CIBMTR's research agenda. It also helps coordinate initiatives for presenting CIBMTR research outcomes to the public. Committee representatives participate annually in the Cellular Immunotherapy for Cancer, Donor Health and Safety, Graft versus Host Disease, Health Services and International Studies, and Late Effects and Quality of Life Working Committees. Members may participate in other committees as needed.

Membership includes a CIBMTR Scientific Director, seven patient representatives (patients, family members, and donors), two Co-Chairs (who serve as ex officio members of the CIBMTR Advisory and Clinical Trials Advisory Committees), and ex officio members. Patient representatives are nominated by center directors and coordinators, recommended by a panel of CIBMTR and NMDP/Be The Match Patient and Health Professional Services department representatives after conducting phone interviews, and approved by the CIBMTR Advisory Committee. Members serve up to two three-year terms, which are staggered to maintain continuity. If elected as Co-Chair, a member may serve one additional three-year term. The Scientific Director provides scientific support and oversight, and the NMDP/Be The Match Patient and Health Professional Services department provides administrative support and subject matter expertise. Ex officio members include:

- CIBMTR Executive Director;
- CIBMTR Chief Scientific Director;
- Executive Director CIBMTR Milwaukee;
- Relevant CIBMTR Working Committee Statisticians;
- CIBMTR and NMDP/Be The Match Marketing and Communications department representatives;
- NMDP Senior Manager, Data and Program Evaluation (Liaison);
- CIBMTR and NMDP/Be The Match Patient and Health Professional Services department representatives and administrative staff;
- HRSA representatives.

The committee meets in person annually at the TCT Meetings and by teleconference as needed.

2.4 SCIENTIFIC WORKING COMMITTEES

Most clinical outcomes research, a core activity of the organization, is conducted under the auspices of 15 scientific Working Committees (**Chapter 6**). Major responsibilities of these committees are specific to their research area and include:

- Reviewing, approving, and prioritizing study proposals that use CIBMTR data;
- Designing and conducting studies that use CIBMTR data, statistical resources, networks and / or centers;
- Periodically assessing and revising sections of CIBMTR data collection forms;
- Planning and conducting workshops at CIBMTR meetings.

Membership on CIBMTR Working Committees is open to any individual willing to take an active role in study development and completion. This includes basic and clinical scientists with expertise in HCT, cellular therapy, and related disciplines as well as Coordinating Center Physicians and Statisticians who work collaboratively with investigators to design and conduct studies. Working Committee leadership positions include:

- Chairs (2-3);
- CIBMTR Scientific Director(s) (1-2);
- CIBMTR Statistical Director (1);
- CIBMTR MS-level Statistician(s) (1-2).

Chairs are experts in their fields and have demonstrated commitment to the work of the CIBMTR. A Coordinating Center administrative staff member requests nominations in spring of each year for Working Committee Chair terms expiring in the following spring. Nominees provide biographical information if they are interested in being considered for the role. Current Working Committee Leadership provides input regarding the nominees, and the Nominating Committee puts forth recommendations to the Advisory Committee. Once appointed, Chairs hold longer, non-renewable, five-year terms to maintain continuity throughout study lifecycles and research agendas.

In the event a Working Committee Chair relinquishes his / her position before the end of the term and within the annual nomination cycle, the replacement will follow the standard election process. If a committee member relinquishes his / her position outside the annual nomination cycle, the position will remain open until it can be filled during the next nomination cycle. Due to the need to maintain staggered terms, the term of the new / replacement committee member will be independently assessed. If possible, a full five-year term will be offered. However, if a five-year term would cause too many Chairs to leave the committee at the same time, the term of this new committee member will end at the date of the original position, and the new member will be eligible for nomination to a second term.

Working Committees meet in person annually during the TCT Meetings, at which time current studies are discussed and new proposals are considered. Teleconferences among Working Committee leaders are held every four to six weeks and may include the Principal Investigators (PIs) of committee studies.

For more detailed information about Working Committees, see **Chapter 6**.

2.5 CONFLICT OF INTEREST POLICY

The CIBMTR Committee Leadership adheres to the CIBMTR Conflict of Interest Policy (POL-0001). The policy includes conflict of interest disclosure requirements and monitoring processes and procedures for CIBMTR's Administrative and Working Committees. A CIBTMR Conflict of Interest Survey (Form-0001) is provided to all Advisory Committee members in January and Working Committee leadership each November. Conflict of Interest disclosure records are

maintained securely on the CIBMTR Milwaukee campus and on a secure network drive. Conflicts are handled as described in the Conflict of Interest Policy (POL-0001).

Additionally, the CIBMTR requires conflict of interest disclosure with research study proposals, presentations, and publications. At the time of journal submission, authors are required to disclose any potential conflict of interest, including but not limited to employment, consultancies, stock ownership, honoraria, paid expert testimony, ownership interests including stock options, and/or membership on another entity's Board of Directors or its Advisory Committee. To do so, they must submit a "CIBMTR Conflict of Interest Disclosure Form" (**Appendix E**) to the CIBMTR Coordinating Center.

CHAPTER 3: AUTHORSHIP

3.1 GENERAL RULES OF AUTHORSHIP

The CIBMTR is committed to the timely completion and publication of research results. The general rules of authorship apply to any investigator or group using information from the CIBMTR Research Database. These qualified individuals may also be required to follow guidelines for developing and completing research studies (**Chapter 4**), submitting proposals (**Chapter 6),** and submitting data (**Chapter 11**). The *rules of authorship* described in this chapter are consistent with The Journal of the American Medical Association (JAMA) Guidelines.

The primary criteria for authorship are commitment and contributory engagement throughout the life cycle of the project. Generally, the person who proposes the study is the study Principal Investigator (PI). An exception might occur if the person proposing a study is not associated with a center or has only a trivial proportion of the cases from his / her center and a member of a center with a large proportion of the patients' requests to lead the study at an early stage (e.g., during protocol development). These rare situations are adjudicated by CIBMTR leadership, including the Working Committee leadership, Senior Scientific Director for Research Operations, and Chief Scientific Director. Most cases are resolved by appointing co-PIs with agreement about authorship order made in advance.

The vast majority of CIBMTR studies require patients with detailed CRF-level data, which affects author-related considerations as detailed below. For more information about data management and CRFs, see **Chapter 11**.

Authorship rules for manuscripts related to a commercially funded project or study follow the same intent as those associated with a Working Committee study where applicable. Authorship will be determined based upon contribution of effort and cases, and a final determination may be delayed until accrual is complete. Other considerations include:

- Most commercial projects will involve sponsor input in manuscript development;
- Rules for authorship may be outlined within the project plan;
- When a steering committee exists, that group will oversee authorship decisions;
- When a steering committee does not exist, CIBMTR leadership will oversee authorship decisions;
- When publication is not included in the sponsored project plan, the study team may still choose to develop a manuscript; however, all CIBMTR oversight requirements must be met, and sponsor input will generally still be required.

3.2 ESTABLISHING THE WRITING COMMITTEE FOR WORKING COMMITTEE STUDIES

3.2.1 Center Volume Assessment

Numbers of patients from each contributing center are included in the materials prepared by MS-level Statisticians during proposal and protocol development; these data are used later to facilitate assessment of the PIs center's level of participation (e.g., data submission) pertinent to that study. Numbers of cases with TED-, CRF-, and CTED-level data submitted are considered for research studies.

If a center that is among the five centers with the largest numbers of cases in the study, or a center that contributes 10% or more of the cases, is not represented on the Writing Committee,

a separate memo is sent to the center director to determine whether the center wishes to designate a representative for the Writing Committee.

3.2.2 Solicitation for Writing Committee Members

An important milestone in the life cycle of a study is the point at which the PIs draft protocol is approved by the Working Committee leadership and undergoes final review by the Coordinating Center. This document is then distributed by the Coordinating Center to all Working Committee members on record. The CIBMTR invites these individuals to participate on the study Writing Committee and requests their comments on the protocol. After soliciting Writing Committee membership interest, Working Committee leadership reviews this participant list as well as the list of centers that contributed data for substantial numbers of patients meeting the eligibility criteria for the study (see above).

The CIBMTR expects everyone who agrees to participate on a Writing Committee to provide timely and substantive contributions to study design, data analysis, interpretation of results, and preparation of the manuscript for publication.

3.2.3 Consideration in Special Situations

- **CIBMTR studies evaluating rare diseases or new and / or novel therapies indications.** Medical Directors of centers that are among the five with the most patients reported, or that have provided the majority of patients reported and included in a study, are solicited to contribute to authorship at the protocol development stage. Authorship will generally be granted to a representative from each of those centers. However, authorship is not guaranteed, and center representatives must make contributions to the study that are consistent with authorship guidelines.
- **CIBMTR studies evaluating cord blood.** Some studies evaluate outcomes of transplantation using cord blood as the graft source, in which graft handling or processing are relevant issues. Representatives from cord blood banks whose graft products are substantially represented in the proposal are eligible for invitation to join the Writing Committee. Scientific Directors and MS-level Statisticians are charged with remaining cognizant of these special cases and extending invitations as appropriate.
- **CIBMTR studies that use biologic samples.** Writing Committees for studies that require the use of DNA samples from the Research Sample Repository operate slightly differently because the PI typically has made a substantial investment in the samples and the testing performed **(Chapter 7).** In these cases, the PI works with the assigned Working Committee Scientific Directors and Chairs to define the Writing Committee at study initiation. The Writing Committee is typically composed of the assigned CIBMTR Working Committee statistical analysis team and collaborators identified by the PI. Writing Committees for these studies may be opened to full Working Committee participation at the request of the PI.

3.3 AUTHOR LIST DEVELOPMENT

As noted above, to assure co-authorship status, members of the Writing Committee must make timely and substantive contributions to study design, execution, data analysis, interpretation of results, and preparation of the manuscript for publication, including any requested changes. Members of the Writing Committee who do not fulfill this requirement are expected to

withdraw as a co-author or, alternatively, their names may be removed by the PI in consultation with the Scientific Director and MS-level Statistician; the MS-level Statistician typically monitors all comments and shares this information with the PI / Scientific Director. This section describes important considerations in the process of compiling author lists.

3.3.1 Number of Authors

Because the number of authors permitted for any given study is sometimes limited by the journal, first authors are encouraged to consider selecting journals where multi-center authorship and journal policy permit multiple authors. The criteria to assist study PIs in making author list decisions are associated with the three major requirements of author contribution: Engagement in protocol development, interpretation of data analysis, and manuscript preparation.

If the total number of authors exceeds the journal maximum, the PI may request that Coordinating Center staff correspond with the journal requesting the inclusion of a few additional individuals on the primary author list. If this is not permitted, the CIBMTR recommends one of the two following options in the "author contribution section" of the manuscript:

- If acknowledging specific individuals, please state as follows: "We would like to recognize and thank the contributing co-authors who assisted substantially in the design and writing of this study including Drs. AAA, BBB, CCC, and DDD."
- If acknowledging the entire Working Committee, please state as follows: "On behalf of the CIBMTR _____ Working Committee".

If a paper is rejected by one journal and resubmitted to another, the author list rules may change, requiring reassessment of the primary author list. In these cases, authors must be notified by the study leadership of changes before submission.

3.3.2 First Author Designation

The study PI is usually the First Author and is typically the person first proposing the study. An exception is if the center of the person proposing a study has provided only a trivial proportion of the cases to be studied and a member of a center with a large proportion of the patients also requests to be PI. These decisions are made prior to initiation of the project (**Section 3.1**), and authorship positions for these individuals are designated at that time. Since most studies include only patients with detailed CRF-level data, this gives preference to investigators from centers submitting CRF-level data (**Chapter 11**).

3.3.3 Authorship Ranking

Authorship ranking is weighted towards committee members who participate in the development of the study and those from centers that have contributed substantial data for the study and helped with study development. Authorship ranking may vary depending on the complexity of a study and overall level of involvement required of Working Committee leadership, including the Scientific Director (often but not always the Corresponding Author) and the Statistical Director. Sometimes authorship is given, on a case-by-case basis, for contributing unique or specialized expertise to a project.

Working Committee Chair status does not automatically guarantee inclusion on the author list of any CIBMTR manuscript. Working Committee Chairs must make substantive contributions to the design, implementation, and interpretation of a study to merit authorship, similar to the measurable requirements for all other authors as noted above.

Working Committee Chairs and Scientific Directors help to adjudicate differences of opinion about authorship with final decision made by the Senior Scientific Director for Research Operations and Chief Scientific Director if necessary.

3.4 CONTRIBUTION EXPECTATIONS

Typically, contributions made to the progress of a study by the PI and / or Writing Committee member, from proposal to journal acceptance, are based on the participation criteria described in this section.

PI responsibilities include:

- Present his / her proposal during in-person Working Committee meeting (held during the annual TCT Meetings) following CIBMTR Coordinating Center guidelines;
- Upon proposal acceptance, return a signed, study-specific Letter of Commitment (**Appendix D1 or D2**) by the deadline noted in the letter (includes co-PIs);
- Assist the Working Committee Chairs and Coordinating Center staff to develop a reasonable timeline for study completion;
- Prepare a first Draft Study Protocol and the Final Study Protocol;
- Participate actively in teleconferences and meetings (e.g., Coordinating Center weekly statistical meetings upon invitation);
- Participate actively in data file preparation and analyses;
- Prepare study materials, as necessary, for submission for meeting presentation;
- Prepare a first draft of the manuscript within 30 days of receiving the final study results;
- Prepare any subsequent manuscript draft within 30 days of prior distribution to the Writing Committee;
- Collate and prepare memos addressing comments of Writing Committee members at protocol, analyses, and manuscript stages;
- Collaborate with CIBMTR Coordinating Center in submitting manuscript or submit per CIBMTR guidelines (**Chapter 4**);
- Address comments from reviewers, with input from Working Committee Leadership and other co-authors;
- Respond to editorial questions and approve galley proofs.

PI and Writing Committee member responsibilities include:

- Engage in the protocol development process as evidenced by substantive and timely comments and suggestions (generally within two weeks of receiving the circulated document or query), particularly regarding scientific merit and / or statistical design;

- Engage in interpretation of data analysis as evidenced by substantive and timely comments;
- Engage in manuscript preparation as evidenced by substantive and timely comments;
- Engage in the journal review process by substantive and timely responses to journal queries and comments.

Corresponding author (often the CIBMTR Working Committee Scientific Director) responsibilities include:

- Participate in determining fair and equitable author ranking per CIBMTR guidelines (see above);
- Communicate with the journal editorial staff, with support from the CIBMTR Coordinating Center;
- Manage communication between co-authors;
- Circulate comments, with support from the CIBMTR Coordinating Center, to all co-authors;
- Coordinate, as point of contact, queries following publication;
- Ensure compliance with CIBMTR and NIH procedures to acquire a PubMed Central ID (PMCID) number*. It is the responsibility of the corresponding / submitting author on any CIBMTR peer-reviewed paper to assure the proper steps are taken by the journal to submit the article to PubMed Central for assignment of a PMCID number. If the accepting journal does not provide this service (many do), the Corresponding Author must do so or should solicit help from the Coordinating Center. This is required of the CIBMTR (by NIH Public Access policy) and is relevant to any peer-reviewed paper that uses data generated by the CIBMTR. For more information, see **Chapter 4**.

3.5 MANUSCRIPT PREPARATION

The PI has primary responsibility for manuscript preparation (SOP-0072: Manuscript Preparation) and is expected to prepare a first draft manuscript within 30 days from completion of the final approved analysis. This draft is then reviewed, revised as necessary, and approved by Working Committee leadership.

The PI ensures that description and interpretation of the statistical analyses are accurate and contributes to the fundamental message of the manuscript. A CIBMTR Administrative Assistant or Coordinator, under the direction of an MS-level Statistician, distributes the first draft manuscript to the pre-identified Writing Committee for their comments.

The PI incorporates relevant comments into a subsequent draft. As with the analysis, this is an iterative process until all involved agree that the manuscript is ready for submission. Writing Committee members generally have two weeks to respond to each circulated draft. The

* This is a US based mandate by the NIH; see **Appendix C** for further details.

approved final draft manuscript is the version submitted to the identified journal. See **Chapter 4** for submission details.

The final author list is determined at this stage since it depends largely on the value and extent of contribution of each individual throughout the study process.

3.6 CIBMTR FACULTY AND STAFF AUTHOR CITATIONS

To standardize the manner in which CIBMTR faculty and staff indicate their respective institutions when they are cited in author lists, the CIBMTR recommends the following formats:

- Faculty: "CIBMTR – Division of Hematology, Oncology, and Transplantation, Department of Medicine – University of Minnesota" or "CIBMTR – Division of Hematology / Oncology, Department of Medicine – Medical College of Wisconsin";
- Staff: "CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI" or "CIBMTR® (Center for International Blood and Marrow Transplant Research), National Marrow Donor Program/Be The Match®, Minneapolis, MN";
- For off-site Scientific Directors, we suggest: "CIBMTR – Division of _____, Department of _____ [name of institution]".

CHAPTER 4: MANUSCRIPT SUBMISSION

Fundamental PI responsibilities during the life cycle of a study are described in this chapter but with focus on the final steps in the process of submitting an approved manuscript to a scientific journal for peer review and publication (SOP-0073: Manuscript Submission).

For additional guidelines and helpful hints for PIs conducting a study with the CIBMTR, see "Guidelines for Study Principal Investigators" in **Appendix B**. These guidelines are provided to each PI upon study acceptance. For more information about authorship, see **Chapter 3**.

4.1 PI RESPONSIBILITIES

The CIBMTR expects active involvement on the part of the study PI to minimize the time from study activation to submission. The time required to move a study forward to manuscript submission depends a great deal on the PI completing the following:

- Read the "Guidelines for Principal Study Investigators" (**Appendix B**);
- Read the "CIBMTR Guidelines for acquiring PMCID Numbers" (**Appendix C**);
- Prepare a first draft of the manuscript within 30 days of receiving the final study results;
- Prepare any subsequent manuscript draft within 30 days of prior distribution to Writing Committee;
- Collate and prepare memos addressing comments of Writing Committee members at protocol, analyses, and manuscript stages;
- Submit a "CIBMTR Conflict of Interest Disclosure Form" (**Appendix E**) to the CIBMTR Coordinating Center;
- Collaborate with CIBMTR Coordinating Center in submitting manuscript;
- Address comments from reviewers, with input from CIBMTR Statisticians and other co-authors;
- Respond to editorial questions and approve galley proofs.

4.2 FINAL SUBMISSION STEPS

4.2.1 Immediate Pre-Submission Phase

The CIBMTR Coordinating Center employs a Medical Writer who, upon request, reviews meeting abstracts and final draft manuscripts prior to journal submission. This review is limited to items such as a check for standardized usage of acronyms and abbreviations, correct grammar and spelling, etc. Upon completion, the reviewed, edited manuscript is then returned (with tracked changes, if any) to the corresponding author, copying the Scientific Director and Study Statistician, for final approval prior to submission by either the corresponding author or by the CIBMTR's Coordinating Center staff.

4.2.2 Manuscript Submission

There are two approaches for submitting manuscripts:

1. CIBMTR Submits the Manuscript (Preferred)

Due to critical NIH requirements for acquisition of PMCID numbers (**Appendix C**) for all published, peer-reviewed works funded by the NIH (e.g., when CIBMTR data are used), the CIBMTR prefers that manuscript submissions and resubmissions be processed centrally. If the

CIBMTR submits the manuscript, the administrative staff requests and uses the username / password of the corresponding author for the relevant journal to complete the submission.

When handled centrally, a CIBMTR Administrative Assistant or Coordinator, under the direction of an MS-level Statistician, submits (using the corresponding author username / password for the specified journal) the approved final draft manuscript to the pre-identified, scientific journal and is responsible for any correspondence with the selected journal's editorial staff during the submission procedure. The corresponding author forwards subsequent editor and reviewer comments to the PI, Scientific Director (if not the corresponding author), and Study Statisticians. The PI is expected to prepare a response within 14 days, working with Coordinating Center staff to obtain additional data analyses if needed.

2. PI / Corresponding Author Submits the Manuscript

If the PI / corresponding author prefers to submit his / her own paper, he / she must agree to follow the required *NIH processes for obtaining a PMCID number*. The CIBMTR provides PIs with proper guidelines (**Appendix C**) at any time upon request and when:

- The "Letter of Commitment" is distributed;
- The manuscript is submitted;
- The manuscript is accepted.

When PIs submit their own papers on behalf of the CIBMTR, they are urged to notify the CIBMTR of the submission (e.g., via the relevant Working Committee MS-level Statistician, central office, etc.) due to the CIBMTR's obligations regarding the NIH Public Access policy.

When a study PI, or collaborating partner group, submits the manuscript, he / she should be reminded by Working Committee leadership of these NIH requirements and of proper acknowledgements (see below). In all cases in which CIBMTR data are used within the study (most cases) and the study PI or a collaborating group member submits the paper, he / she should, throughout the process, respond "yes" when asked to confirm NIH funding. The grant is #U24-CA76518-"current funding cycle year" (automatically displayed), and Mary Horowitz, MD, MS, is the PI for this grant. Her name is automatically associated with the grant number in the NIH Manuscript Submission procedures when a paper is accepted and submitted to PubMed Central.

4.2.2.1 Additional Submission Requirements

Regardless of who submits the manuscript, submission documents should include the following:

- "CIBMTR Data Sources" statement (**Appendix F**);
- Current "CIBMTR Support List" (**Appendix G**);
- Acknowledgement of NIH funding (i.e., "CIBMTR NIH Support Verification Letter") (**Appendix H**). The Medical College of Wisconsin recommends that, to maintain compliance with NIH Public Access policy, whoever submits the paper should also submit an "NIH Support Verification Letter" at the time of submission to alert the editor that the paper qualifies as one that must be made available to the public via PubMed Central.

Current versions of these documents are available to PIs or other submitting groups upon request to the central office. They are maintained at the Coordinating Center Milwaukee

Campus (414-805-0700), updated periodically, and approved by the Executive Director in Milwaukee and the Vice President for Research Operations in Minneapolis.

4.2.2.2 Journal Submission to PubMed Central

Most, but not all, journals to which the CIBMTR submits research papers forward the final peer-reviewed manuscript or the final published article to PubMed Central. There are a variety of submission methods available to journals and authors; review *the NIH When and How to Comply Public Access Policy* or *the National Center for Biotechnology (NCBI) Navigating the National Institutes of Health Manuscript Submission (NIHMS) Process* for specific directives depending on the journal to which the paper is being submitted. The submission method specifies which manuscript version is permitted. The version options are:

- **Final peer-reviewed manuscript.** The investigator's final manuscript of a peer-reviewed paper accepted for journal publication, including all modifications from the peer review process.
- **Final published article.** The journal's authoritative copy of the paper, including all modifications from the publishing peer review process, copyediting and stylistic edits, and formatting changes.

If the journal does not offer this submission service, the corresponding author has primary responsibility for doing so using Method D, as described on the websites linked above. The CIBMTR Coordinating Center can also submit on behalf of the corresponding author by using Method C.

Also see *Frequently Asked Questions about the NIH Public Access Policy.*

4.3 PUBLICATION LISTS

CIBMTR publications are posted online monthly. Listings date back to inception of the IBMTR in 1972. Beginning in January 1, 2010, the publication list also includes articles published by the NMDP/Be The Match dating back to its inception in 1987 as well as statistical methodological papers authored by CIBMTR partner PhD-level Statisticians. All works since the 2004 affiliation of the IBMTR and NMDP (**Chapter 1**) are identified as CIBMTR publications.

To accommodate frequent and assorted reporting requirements, information is maintained internally to monitor numerous data elements relevant to CIBMTR publications (authors, author institutions at time of publication, grant information, duration of study lifecycle to time of publication, journal impact factors, etc.). This internal, comprehensive *publications document* is updated monthly and available to both campus staff members on Collaborate.

CHAPTER 5: STATISTICAL RESOURCES

5.1 COLLABORATION WITH THE MCW DIVISION OF BIOSTATISTICS

Since 1985, the CIBMTR has benefitted from a unique and collegial partnership with PhD Biostatisticians from the MCW Division of Biostatistics in the Institute for Health and Equity. This distinctive relationship contributes substantially to the CIBMTR's success. The collaboration is funded in part by an NCI grant and the SCTOD contract (**Chapter 6**). The MCW Biostatistics Division mission is threefold:

- Provide basic biostatistical support to MCW's community of biomedical researchers;
- Commit to high-quality research in statistical methods;
- Commit to its PhD program in biostatistics.

This long-standing association between the CIBMTR and MCW Division of Biostatistics faculty:

- Ensures the statistical integrity of CIBMTR scientific activities;
- Results in articles on statistical issues related to HCT and cellular therapy for clinical audiences;
- Supports Working Committee members and investigators in developing scientific study protocols using CIBMTR data and provide multivariate analysis for each study.

The MCW PhD Faculty Biostatisticians who work with the CIBMTR have substantial experience in assessing the unique statistical problems associated with HCT and cellular therapy. They collaborate with CIBMTR MD Scientific Directors (most also hold MS degrees in statistics, epidemiology, or public health) and network investigators in each of the CIBMTR Research Programs. In addition, the PhD Biostatisticians have developed an active Statistical Methodology Research Program investigating new approaches and techniques for analyzing HCT and cellular therapy data. Finally, during the annual TCT Meetings, the PhD Biostatisticians host a statistics session focusing on statistical design and analysis. In addition, they provide 1:1 statistical consultation to researchers writing proposals or developing protocols for CIBMTR studies.

The CIBMTR Coordinating Center directly employs more than 20 MS-level Statisticians, some with more than 10 years of experience with HCT studies. The MCW PhD Biostatisticians are significantly involved in training these MS-level Statisticians, overseeing ongoing studies, and collaborating with them on the univariate and multivariate analyses.

Following is a detailed description of how the Division of Biostatistics integrates with the mission of the CIBMTR to improve the outcomes of HCT and cellular therapy.

5.1.1 Biostatistics Leadership

The MCW PhD Biostatisticians are Statistical Directors within the CIBMTR organizational structure and report directly to the CIBMTR Chief Scientific Director. In addition to the Chief Statistical Director, eight PhD Statistical Directors from the MCW Division of Biostatistics participate in CIBMTR research activities under a part-time, subcontracted arrangement with the following focus:

- Lead Statistician for the BMT CTN and as a Statistical Consultant to the NMDP/Be The Match; this person led the statistical development approach for NMDP/Be The Match's current center-specific analysis (now the purview of the CIBMTR);
- Survival analysis and expertise in analysis of HCT and cellular therapy data that involve censored and / or truncated time-to-event data and competing risk events;
- Research with an emphasis in statistical genetics, and this person provides statistical service for analyzing immunogenetic data (**Chapter 7**);
- Other expertise in biostatistics and support of CIBMTR research in their respective focus areas;
- Occasionally visiting professors also participate in analysis of CIBMTR data.

The CIBMTR Program Director of Clinical Outcomes Research and Statistical Operations leads the MS-level Statistical team and provides overall statistical oversight, coordination, and training for the CIBMTR Scientific Working Committees (**Chapter 6**) as well as most statistical coordination within the other CIBMTR Research Programs (**Chapters 7-10**)**.** The Program Director of Clinical Outcomes Research and Statistical Operations works in collaboration with the Senior Scientific Director for Research Operations and Chief Statistical Director.

5.2 STATISTICAL METHODOLOGY

The Chief Statistical Director and his staff actively participate in the development and adaptation of statistical methodology for optimal analysis of the CIBMTR and other transplant- and cellular therapy-related data. This group has expertise in survival analysis and publishes methodological papers that address issues in the analysis of post-HCT outcomes.

The CIBMTR has an important role in guiding the research community in appropriate application and interpretation of sophisticated statistical models required for analyzing HCT and cellular therapy survival data. Thus, CIBMTR statistical research is twofold: Development of new statistical methodologies and subsequent application of these methodologies to studies using CIBMTR clinical data.

The most common outcomes of interest being studied are hematopoietic recovery, acute and chronic graft-versus-host disease (GVHD, the most important obstacle to a successful outcome), transplant-related mortality, disease recurrence, and disease-free and overall survival.

HCT and cellular therapy are complex procedures with multiple competing risks; therefore, analyzing outcomes can pose statistical challenges that are not amenable to standard methods. The post-therapy period, in particular, is complex to model with patients transitioning between numerous states. These include episodes of engraftment, GVHD, relapse, application of post-treatment therapies, and occurrence of secondary cancer. In some analyses, models fit on final outcomes must be synthesized with models fit on intermediate events in order to derive a model that predicts patient outcomes based on their history at a particular point in time. Censoring, through loss to follow-up, and truncation, through delay entry, further complicates analyses.

Statistical challenges are numerous. The common competing risks problem results when the occurrence of one outcome (e.g., death from regimen toxicity) precludes occurrence of another (e.g., relapse). Another challenge with data analysis is that covariates, such as GVHD or immune

suppressive treatment, may change over time. When comparing HCT or cellular therapy to other therapies, it is necessary to consider differential start times for the treatments, using statistical adjustments such as delayed entry into the study cohort or time-dependent stratification.

These statistical problems require development or extension of new statistical tools by investigators with expertise in both the clinical and statistical problems of HCT. This is the unique feature provided by the CIBMTR Statistical Directors.

Certain methodology approaches are required or must be considered for analyzing survival data in the CIBMTR Research Database, including:

- Competing risks;
- Multistate models;
- Techniques for censored and truncated data;
- Clinical trials design.

These data are often used to teach clinicians and other researchers how to properly analyze such complicated information. Lessons include descriptions of results in various disease states and patient groups, determining prognostic factors (including immunogenetic factors), defining inter-center variability in diagnosis, practice and outcome, and evaluating long-term outcomes including quality of life, and developing analytic approaches to evaluating outcomes.

5.2.1 Comparative Approaches in HCT and Cellular Therapy

As noted above, reliably assessing outcomes is complex. Outcomes are influenced by many patient- and disease-related factors such as age, disease stage, and prior treatment as well as transplant-related factors such as graft source, conditioning regimen, and GVHD prophylaxis. The CIBMTR addresses issues in large randomized clinical trials, but clinical trials present specific challenges related to transplantation and cellular therapy. (The CIBMTR Clinical Trials Support Program is presented in **Chapter 8**.) For example, enrolled patients may represent only a small proportion of the target population and may not be representative of the larger group. Also, most clinical trials focus on short-term and intermediate-term outcomes, yet there is need for long-term follow-up of recipients since HCT and cellular therapy may be associated with important effects, such as therapy-related cancers, which occur many years after treatment. The CIBMTR leverages its Research Database to conduct studies that address these challenges after cautious interpretation and acknowledgment of methodological restrictions.

This research can also be used to evaluate new regimens and compare transplant and cellular therapy with other therapies. Results of various strategies among concurrently treated patients using observational data can be compared, provided that appropriate adjustments are made to ensure that comparable patients receiving the alternative strategies are evaluated. The CIBMTR Statistical Directors analyze the detailed clinical information for each patient, allowing adjustment for potentially confounding effects of important prognostic variables. To compare the results of different treatment regimens, their approach is to:

- Define the therapies to be compared;
- Compare the characteristics of patients treated with each therapy;

- Compare the results after adjusting for variables that differ significantly among the treatment groups.

This adjustment can be done either by stratifying important prognostic factors, matching for important factors or propensity scores, or multivariate regression. The approach is dependent on the outcome, the explanatory variables to be evaluated as well as the size of the population to be studied. Sometimes all of these techniques are used to demonstrate that the results are not dependent on a particular method.

In some instances, HCT or cellular therapy is used to treat diseases where there is no other effective therapy. Often, large randomized trials are not possible in these instances due to the rarity of the disease; variable treatment philosophies; and the limited availability of donors, technologies, and resources. There are also other potentially curative treatments that raise the question of relative effectiveness. It is difficult to compare published results of HCT and cellular therapy versus other treatments directly. Differences in patient selection and inherent delay in performing treatments can lead to truncation of early failures from most series (time-to-treatment bias).

Comparisons of HCT or cellular therapy to alternative treatments can be done by combining CIBMTR data with primary data compiled by groups studying other regimens. These comparisons use regression or matching techniques to adjust for patient differences. They handle time-to-treatment differences in a variety of ways, all of which have the net effect of giving less weight to events occurring at a point in the disease when few patients have proceeded to transplant. Coordinating Center personnel have conducted simulation studies to compare methodologies for conducting these studies.

Comparing treatments, whether they are different HCT or cellular therapy regimens or compared to chemotherapy in non-randomized studies requires careful consideration of potential biases, not all of which can be addressed by statistical techniques. There are limitations to this approach, and the Statistical Directors address potential biases in presentations of results. However, such studies contribute to understanding treatment effects, provide valuable data for planning and interpreting trials, and, in some situations, are the only feasible means of comparing strategies in a controlled fashion.

5.3 CIBMTR BIOSTATISTICAL ACTIVITIES

5.3.1 CIBMTR Working Committee Support

The primary way in which the Statistical Directors oversee and influence the integrity of CIBMTR data analysis is in their role as members of the Working Committees. They guide the analytical assessment of data extracted from the large database that are relevant to the scientific question(s) of each ongoing study.

Statistical meetings are held weekly and attended by all Scientific Directors, Statistical Directors, Coordinating Center Statistical Staff, and, in most cases, study PIs and Working Committee Chairs. During the meeting, attendees discuss protocol design, selection of the study population, proper variables and those that need to be adjusted in the analysis, and the approach to statistical analysis. The Statistical Directors are available to the members of their Working Committees for in-person or phone consultation, and they attend monthly teleconferences of their assigned Working Committee leadership meetings. The Statistical

Directors approve univariate analyses completed by the MS-level Statisticians and perform the multivariate analyses for each study. Scientific Directors and assigned Statistical Directors work closely with study PIs during all phases of study development including final approval of the manuscript that is submitted to peer-reviewed journals for publication.

The Immunobiology Working Committee (**Chapter 7**) has a unique and independent mission. It addresses scientific questions about the association between genetic factors and successful transplantation outcomes. The committee's studies include comparisons of clinical outcomes from different donor types (e.g. mismatched related versus unrelated donors).

5.3.2 Center-Specific Analysis

Though NMDP/Be The Match has been analyzing center outcomes for unrelated donor HCTs since 1994, these analyses are now under the purview of the CIBMTR as required by the SCTOD contract (**Chapter 6**), and they now include data on related donor HCTs. Reports provide one-year survival statistics for all US centers doing allogeneic HCT, both related (since 2008) and unrelated, using a three-year rolling window. The reports compare observed and expected survival rates with a 95% confidence interval. Because centers vary considerably in the risk level of the cases they treat, the CIBMTR developed a statistical model to adjust for risk factors known or suspected to influence outcomes. Reports are submitted to HRSA each year, and copies are distributed to center medical directors and payers. Results are published on the Be The Match *Transplant Center Search webpage*. These reports are useful for improving quality of HCT and informing the public about them.

Since 2008, the CIBMTR has conducted biennial forums to discuss and develop plans to conduct these center-specific survival analyses with center representatives and experts in outcomes reporting and statistical analysis as well as patient and payer representatives. The last forum was held in September 2018. Recommendations generated during these forums are used to guide the center-specific survival analyses. These recommendations are distributed to US center medical directors and made available on the CIBMTR *Center Outcomes Forum* webpage.

5.3.3 Public Website Display of Survival Data

As part of the SCTOD contract, the CIBMTR provides information about related and unrelated allogeneic transplants performed by US centers. Data on autologous transplants are submitted voluntarily by centers and are also included in these reports. The reports provide a moving five-year window of data:

- ***US Patient Survival Report***. Published approximately every three years, this report provides patient survival estimates by disease at the following time points after transplant: 100 days, 1 year, and 3 years. Survival estimates are also available by patient age, patient gender, patient race, cell source, and the year the transplants were performed.
    - The window for these data includes five years of "accrual" into the cohort and three years of follow-up.
    - Sample sizes for some categories are quite small, so statistically valid estimates of overall survival outcome cannot be calculated where there is not enough patient data available for analysis.

- ***US Transplant Data by Center Report***. Published annually, this report provides the number of bone marrow and cord blood transplants performed at a specific center for various diseases and donor types over a five-year time period.
- ***US Transplant Data by Disease Report***. Published annually, this report provides the number of bone marrow and cord blood transplants reported for a specific disease over a five-year time period. Data are also available by patient age, patient gender, patient race, cell source, and year the transplants were performed.
- ***Transplant Activity Report*****.** Published annually, this report provides tables with the number of transplants performed at US centers. These data include all types of transplants, categorized by patient's age, cell source, disease, donor type, gender, race, state of center, and year of HCT.

5.3.4 BMT CTN and RCI BMT

A CIBMTR designated Statistical Director plays a lead role in the activities of both the BMT CTN and RCI BMT, which comprise the CIBMTR Clinical Trials Support Program (**Chapter 8**). A Statistical Director is assigned to each clinical trial, and a MS-level Statistician is assigned to each RCI BMT study. The statisticians are responsible for the design and analysis of that trial, the sample size, power calculations, data analysis, and interpretation. They provide this support throughout the course of the study. Designing clinical trials that produce meaningful results requires that special consideration be given to sample size; eligibility criteria; multiple, competing outcomes; center effects (e.g., those affecting patient outcomes due to practices / approaches unique to center transplant teams); early stopping guidelines; and other issues. Adequate sample sizes are needed to detect meaningful differences in treatment strategies. Selecting eligibility criteria that control for the heterogeneity of the patient population while allowing for reasonable patient accrual is also essential. Using the CIBMTR Research Database, Coordinating Center personnel explore the effects of specific eligibility criteria on the potential for enrollment in clinical trials. The Database is also used in trial design and when considering amendments to enhance accrual.

Assessing multiple, competing outcomes can be challenging, as they can also interfere with assessment of the primary endpoint of a trial. Center effects, which can confound statistical analyses, are particularly important when evaluating complex treatments like HCT and cellular therapy, in which substantial differences in supportive care-related practice patterns among centers exist (e.g., prophylactic and preemptive therapy for infection, nutritional support, isolation practices). Study data is stratified by center whenever feasible to minimize center effects on study results.

Detailed study design and analysis plans vary from the larger Phase II-III trials (randomized or not) to the smaller Phase I-II studies. In both cases, the CIBMTR Research Database provides fundamental data for use by the Statistical Directors in developing and designing these trials.

5.3.5 Health Services Research

The CIBMTR HSR Program (**Chapter 9**) also benefits from the statistical expertise of the Coordinating Center in conducting HCT-related research. The Senior Scientific Director, Senior Manager, Investigator, and MS / PhD level analysts of the HSR Program collaborate with Statistical Directors in a variety of studies.

Representative examples of studies accomplished through this unique initiative, in partnership with the Statistical Directors, are:

- Health economic outcomes research;
- Treatment decision-making support;
- Survivorship and patient-reported outcomes.

CHAPTER 6: CLINICAL OUTCOMES RESEARCH

Clinical outcomes research using the CIBMTR Research Database is a core activity of the organization. These studies address a wide range of issues, focusing on questions that are difficult or impossible to address in single-center studies or randomized trials because diseases treated with HCT and cellular therapy are uncommon and single centers treat few patients with a given disorder. Additionally, clinical outcomes research databases facilitate long-term follow-up permitting studies addressing quality of life and late effects of HCT and cellular therapy.

Clinical outcomes research focuses on the effects of HCT and cellular therapy on recipients and donors as well as the clinical and treatment factors influencing the effectiveness of the therapy. The CIBMTR adheres to a high standard of scientific and statistical rigor in selecting, planning, and conducting observational research, as described in this chapter.

See **Chapter 11** and **Chapter 14** for more information about the CIBMTR Research Database.

6.1 CIBMTR SCIENTIFIC WORKING COMMITTEES

The CIBMTR conducts most clinical outcomes research under the auspices of 15 Scientific Working Committees, listed in **Table 6.1** below. Members include assigned Coordinating Center leadership and staff (discussed further in this section) as well as basic and clinical scientists with expertise in HCT and related disciplines. The major responsibilities of Working Committees are to:

- Review and rank study proposals that use CIBMTR data relevant to the committee's subject area and assist leadership in the proposal approval process;
- Design and conduct studies relevant to their subject area involving CIBMTR data, statistical resources, networks and / or centers;
- Periodically assess and revise relevant sections of CIBMTR data collection forms;
- Plan and conduct workshops at CIBMTR meetings.

Working Committees meet in person annually during the TCT Meetings (**Chapter 16**), at which time current studies are discussed and new proposals are presented and considered using a ranking mechanism standardized by the CIBMTR (**Section 6.1.5.1**).

6.1.1 Working Committee Leadership and Staff

Membership in Working Committees (**Table 6.1**) is open to any individual willing to take an active role in the development of studies using CIBMTR data and / or resources.

6.1.1.1 Chairs

Each Working Committee is generally staffed with two to four Chairs who are appointed by the Advisory Committee to non-renewable, five-year terms. Five-year terms allow Chairs to become familiar with their role, provide continuity over time, and increase the likelihood of guiding studies from proposal to manuscript submission or acceptance for publication. Terms are staggered to facilitate succession while maintaining continuity. Individuals may serve as Chair more than once but not consecutively on the same Committee. Active Chairs are expected to participate in the nomination process for replacement positions with special consideration given to more junior investigators to promote ongoing leadership for the work of the CIBMTR.

Table 6.1. Scientific Focus of CIBMTR Working Committees

Working Committee	Scientific Focus
Acute Leukemia	HCT for acute leukemia and pre-leukemia
Cellular Immunotherapy for Cancer	Non-transplant uses of hematopoietic stem cells
Chronic Leukemia	HCT for chronic leukemias, myelodysplastic disorders, and myeloproliferative disorders
Donor Health and Safety	Donor safety and outcomes
Graft Sources and Manipulation	Graft types, composition, and manipulation techniques
Graft-Versus-Host Disease	Biology, prevention, and treatment of GVHD and its complications
Health Services and International Studies	Social and economic barriers to HCT and cellular therapy access, including quality of care and the influence of psychosocial factors on outcomes, as well as international issues and differences in HCT and cellular therapy
Immunobiology	Histocompatibility and other genetic and immunologic issues related to HCT
Infection and Immune Reconstitution	Prevention and treatment of post-transplant infections and issues related to recovery of immune function
Late Effects and Quality of Life	Long-term survival after HCT and cellular therapy, including clinical and psychosocial effects of treatment
Lymphoma	HCT for Hodgkin and non-Hodgkin lymphoma
Pediatric Cancer	HCT for childhood leukemias and other issues related to use of HCT in children
Plasma Cell Disorders and Adult Solid Tumors	HCT for multiple myeloma and other plasma cell disorders as well as solid tumors in adults
Non-Malignant Diseases	HCT and cellular therapy for non-malignant diseases, including autoimmune diseases, inherited and acquired marrow failure, hemoglobinopathy, immunodeficiency diseases, and inborn errors of metabolism
Regimen-Related Toxicity and Supportive Care	Preparative regimens, prevention, and treatment of early non-GVHD toxicities; supportive care in the early post-transplant period

Chairs are selected for expertise in their topic area as well as to ensure adequate expertise with cellular therapy, including both autologous and allogeneic transplantation, and adequate experience with CIBMTR activities. In general, Chairs must be members of CIBMTR centers that submit CRFs unless an exception is granted by the Advisory Committee. Exceptions are granted to allow individuals without an association with a center but with demonstrated expertise and

commitment to serve as Chair (e.g., PhD Director of a histocompatibility laboratory, apheresis center, or donor registry).

Working Committee Chairs are responsible for facilitating the committee research portfolio to ensure its highest possible quality. This is accomplished through familiarity with all committee studies, the CIBMTR data collection forms, and knowledge of key variables that are typically used in CIBMTR research studies. Chairs demonstrate leadership throughout the year to guide studies, encourage PIs to meet expected timelines and keep the portfolios moving forward. In addition, Working Committee Chairs represent their committee to a wider audience through the committee reports section of the CIBMTR Newsletter (**Section 15.4.9**).

Working Committee Chairs lead the annual TCT Working Committee Meetings. Chairs are expected to be present and provide direction to the discussion so that it is productive and respectful and encourages new member involvement. In preparation for the TCT Meetings, Chairs participate in conference calls with CIBMTR scientific and statistical staff to review proposals, protocols, discuss / finalize the agenda, and plan the Working Committee session; they also participate in the Coordinating Center pre-TCT call with all Chairs and attend the CIBMTR Leadership Reception at TCT. Immediately after the TCT Working Committee Meetings, Chairs meet with the Scientific Director and Statisticians to prioritize the studies (ongoing and proposed) and discuss the assignment of Coordinating Center hours. A significant responsibility of a Chair is to recommend specific Working Committee portfolio studies to be targeted for abstract submission at national and international meetings.

While study PIs hold ultimate responsibility for their studies, every 4-6 weeks Working Committee Chairs lead committee conference calls and communicate via email to shepherd the Working Committee portfolio of studies through the process. Chairs provide thoughtful and expert input on specific study issues. They review the Committee's studies as they progress from concept to proposal and on to analysis and manuscript submission. Throughout this process, they provide timely input to study PIs. If a study stalls, Working Committee Chairs intervene directly with a PI. When a study from their Working Committee portfolio is being presented, the Chair attends and participates in the CIBMTR Statistical Meeting teleconference. Working Committee Chairs are expected to attend a minimum of 80% of all meetings and teleconferences. If this criterion is not met and repeated attempts to reconcile the issue have failed, the Working Committee Scientific Director may ask the Executive Committee to consider appointing a new Chair. In collaboration with the Working Committee Coordinating Statistician and Scientific Director, Chairs are responsible for facilitating and approving meeting minutes of in-person meetings and teleconferences.

If forms relevant to the Committee's area of interest are under revision, Chairs are asked to participate in the new form development process, review content, and agree with changes before the form is finalized. Chairs provide input and review any study specific supplemental data request. Chairs are also asked to consider important study questions that have not yet been suggested. Developing new projects as well as recruiting new investigators is an important aspect of the Working Committee Chair role. Chairs should make every effort to involve a wide group of committee members as PIs and spread both the work and the rewards.

6.1.1.2 Scientific Director

Each Working Committee is assigned a Scientific Director. Scientific Directors are generally active HCT and cellular therapy physicians with Master's level training in biostatistics or a related area. The Scientific Director provides medical oversight and analytic expertise for committee activities and facilitates communication among investigators, Chairs, and the statistical faculty and staff.

6.1.1.3 Statistical Director

PhD faculty members of the MCW Division of Biostatistics provide biostatistical support for all the CIBMTR's scientific efforts (**Chapter 5**). The Chief Statistical Director assigns one Statistical Director to each Working Committee. Statistical Directors participate in all committee meetings / calls and provide guidance in study design. They participate in weekly Coordinating Center meetings to critique statistical methodology and data interpretation during various milestones in the progress of each study. They perform most multivariate analyses for CIBMTR clinical outcomes studies and participate in the MS-level Statistician training program.

6.1.1.4 MS-level Statisticians

MS-level Statisticians on both campuses coordinate the activities of Working Committees, prepare data sets, and perform analyses for individual studies. Each Working Committee is assigned an MS-level Statistician, with a specific number of work hours for committee activities allocated by the Senior Scientific Director for Research Operations in consultation with the Program Director of Clinical Outcomes Research and Statistical Operations. MS-level Statisticians are responsible for:

- Serving as primary Statistician for at least one scientific Working Committee, including developing a timeline for each committee study and monitoring its progress in collaboration with Working Committee Chairs and Scientific Directors, setting up teleconferences with Working Committee Chairs, and communicating with the PIs;
- Directing approximately 10-15 studies of HCT and cellular therapy patient data, including preparing the study data set, performing univariate and occasionally multivariate analyses, and assisting in preparing the manuscript;
- Preparing materials for annual Working Committee in-person meetings;
- Responding to external requests for transplant- and cellular therapy-specific information;
- Creating CIBMTR standard reports, such as the Summary Slides and Report of Survival Statistics for Blood and Marrow Transplants;
- Collaborating with the IT programming staff to maintain the integrity of the Research Database variables.

6.1.1.5 MS-level Statistician Training

The Coordinating Center maintains a formal training program for MS-level Statisticians to ensure uniform procedures in the coordination of Working Committee's requests and research study implementation. The training program, which includes workshops led by CIBMTR PhD-level Statisticians and Physicians, focuses on the following areas:

- Overview of HCT and cellular therapy (e.g., common indications for treatment, conditioning regimens, general outcomes, and other disease-specific topics);

- Organizational structure of the CIBMTR [includes standard operating procedures (SOPs)];
- CIBMTR data collection processes;
- Use of and access to TED and CRF databases;
- Information requests and rules for releasing CIBMTR data;
- Preparation for national and international professional meetings;
- Working Committee coordination, management, and written communications;
- Procedures to perform a research study at the CIBMTR;
- Evaluation of proposals;
- Study protocol development;
- Supplemental forms development;
- Data file preparation;
- SAS codes library;
- Definition and analysis of transplant outcomes;
- Completeness index for evaluating adequacy of follow-up;
- Statistical methods of survival analyses (e.g., cumulative incidence function, proportional hazards regression, adjusted survival curves, completeness index, logistic regression, propensity score)
- Univariate and multivariate statistical analyses using *SAS software*;
- Presentation and summary of results;
- Manuscript preparation and submission;
- Research Sample Repository resources and HLA-typing;
- FormsNet and SQL access to research database;
- TCT Meetings overview and preparation;
- CIBMTR Master List of Studies.

Comprehensive educational manuals are provided to each MS-level Statistician for their personal reference. A code library is maintained on SharePoint; the CIBMTR Data Sharing to Non-CIBMTR or Non-NMDP Employees SOP (SOP-0069) details the specific steps in this process.

A Senior Statistician is assigned to junior staff members to provide mentoring and answer questions. There is also a monthly bi-campus MS-level Statistician meeting to discuss updates on Working Committee management, study issues, SAS codes, policies and procedures, data, and other issues as needed. As part of their continuing education, MS-level Statisticians attend annual CIBMTR data management meetings, the annual TCT Meetings, and short courses on statistical techniques that can be applied to the field of HCT and cellular therapy.

The educational manual, MS Biostatistician Reference Guide, developed and maintained by the Program Director of Clinical Outcomes Research and Statistical Operations, is updated periodically and used primarily as a resource tool for the MS-level Statisticians while in training and thereafter. It is available to anyone upon request.

6.1.2 Working Committee Metrics

The CIBMTR Advisory Committee (**Section 2.2.2**) reviews Working Committee metrics three times annually. A dashboard is created for each Working Committee to assist as the Advisory Committee reviews:

- Annual Working Committee Overview and Project Plan report summarizing standard metrics related to Working Committee efficiency;
- Standardized rating systems used at Working Committee meetings to evaluate new proposals and re-evaluate those previously approved studies not yet initiated;
- Annual standardized study impact factor assessment (by Working Committee leadership);
- Annual characterization (by Working Committee leadership) of new studies by major topic, methodology type, and scientific merit to facilitate continuous review of Working Committee portfolios;
- Monthly reports to Working Committee leadership to identify study-specific delays, when appropriate.

Standard Working Committee metrics include the following:

- Process Metrics:
    - Working Committee leadership creates an annual Working Committee Overview and Project Plan with a clear division of labor and responsibilities about leadership.
    - Working Committee leadership evaluates responses to questionnaires regarding the effectiveness of their committee's annual meeting at the TCT Meetings.
    - Working Committee leadership (including Chairs, Statisticians, and Scientific Directors) holds bimonthly calls as documented by brief, action-oriented minutes.
    - Working Committee leadership adequately prepares for and holds face-to-face meetings before and after the committee's annual meeting at the TCT Meetings.
- Productivity and Impact Metrics:
    - Study Progress:
        - Time from study start to manuscript submission <12 months.
        - 80% of the studies within the Working Committee portfolio achieve ≥1 milestone.
        - Total number of studies in progress >3 years is <20% of the portfolio.
    - Manuscript Submission:
        - Total number of submitted papers is >75% of planned submissions.
        - Very low tolerance for manuscripts in preparation >1 year.
    - Publications:
        - Number of publications;
        - Impact factors of journals in which manuscripts published;
        - Relative citation ratios and total number of citations.
    - Presentations:
        - Number of abstracts presented at conferences.

6.1.3 Master Study List and Statistical Hour Allocation

A fundamental resource of the CIBMTR is its Research Database, developed through the collaboration and good will of a very large segment of the HCT and cellular therapy community over a period of more than 40 years. An equally important resource is the statistical support provided to investigators to allow them to use the Research Database to address important issues in HCT and cellular therapy. Although some investigators have local statistical support available for studies, most rely on CIBMTR Statisticians for study design, implementation, and interpretation. Statistical support is a limited resource and must be allocated based on need and merit (SOP-0152: Time Tracking). Experience shows that each study requires approximately 330 statistical hours to complete if not requiring supplemental data or form development. The average number of statistical hours required for each study phase, based on estimates of past CIBMTR studies, is shown below:

- Form development (for studies requiring supplemental data): 40 hours;
- Data collection (for studies requiring supplemental data): 20 hours;
- Protocol development: 100 hours;
- Data file preparation: 100 hours (140 hours if CIBMTR data are to be combined with an external database);
- Analyses: 60 hours;
- Manuscript: 50 hours;
- Submission and response to reviewers: 20 hours.

Prior to the TCT Meetings, Statistician hours for the next academic year are allocated to each Working Committee by the Senior Scientific Director for Research Operations. These allocations depend on the number of available MS-level Statisticians, number of studies in progress and proposed studies, availability of supplementary funding, Working Committee productivity, and overall activity. An initial estimate of hours required for new studies to be proposed to the Working Committee is also made prior to the TCT Meetings. The Working Committee leadership and staff prioritize proposals and studies in progress and determine study timelines based on these allocated hours.

A Master Study List is maintained throughout the year tracking all observational study titles, numbers, Chairs, assigned Statisticians, allotted hours, current status, fiscal year (July 1-June 30) remaining hours, hours remaining to completion, dates that milestones are achieved to measure progress, and more. This is updated three times per year by the Program Director of Clinical Outcomes Research and Statistical Operations in consultation with the Senior Scientific Director for Research Operations and Chief Scientific Director. Studies remain on the list until published or officially dropped. As new proposals are accepted, they are assigned a study number and inserted on the list. Studies may be deferred for a variety of reasons (e.g., pending accrual, requiring supplemental data, financial support, etc.) These studies remain on the list and are reassessed annually. The time to completion of observational studies is a key performance metric of the CIBMTR, with a goal of completing all studies within 18-24 months from initiation.

The Master Study List represents the CIBMTR's research agenda and is reviewed three times annually by the Advisory Committee. This committee provides the highest level of oversight for

study progress and Working Committee activities in general. It makes recommendations as needed to Working Committee leadership.

6.1.4 Statistical Meetings

CIBMTR Scientific and Statistical Faculty and Staff members meet regularly by teleconference to assess active studies and new proposals. These weekly, one-hour sessions are attended by all Scientific Directors, Statistical Directors, and MS-level Statisticians. Working Committee Chairs and Study PIs for studies to be discussed are also invited and frequently attend. The Program Director of Clinical Outcomes Research and Statistical Operations approves the meeting agenda for presentation using the following study-ranking schema:

- Study presentation requires a second review based on recommendations from a previous meeting (highest priority);
- Multivariate analysis is complete, and results are to be distributed to the Writing Committee;
- Protocol is ready for distribution to the Working Committee (this generally includes a preliminary description of the data file);
- Study proposal requires review if Working Committee leadership feels additional input is needed.

Generally, only three studies are evaluated per meeting to permit adequate time for discussion. Studies must be approved by the Statistical Director and Scientific Director before being referred to the Coordinating Center weekly statistical meeting. Relevant study materials (e.g., protocol documentation, descriptive / univariate / multivariate analyses, summaries of findings, and specific questions) are distributed with the agenda four business days in advance of each meeting.

Study PIs are encouraged to attend these meetings to present their study, highlight specific issues, and participate in the statistical discussion. The Scientific Director for the relevant Working Committee presents the study if the PI is unable to attend. The assigned Statistical Director presents results of multivariate analyses. One of three actions may follow the discussion:

- **Protocol is approved for release to the Working Committee.** The protocol will be sent to the Working Committee as-is or after implementing minor recommendations.
- **Limited review is recommended.** The Statistical Director or MS-level Statistician will implement recommended changes. These changes will be reviewed by the Working Committee Scientific Director, Statisticians, and PI, who will either approve distribution of the results to the Writing or Working Committee or will request a second discussion at the Coordinating Center weekly statistical meeting.
- **Another Statistical Meeting review is required.** Major changes will be made, and a subsequent Coordinating Center review will be scheduled within one month of initial presentation.

Each study is presented at least twice at the Coordinating Center weekly statistical meetings: Before finalization of the study protocol and before release of final results. When necessary, additional Coordinating Center weekly statistical meetings are scheduled to ensure timely

discussion of studies and other business. The CIBMTR Statistical Meetings SOP (SOP-0068) details the specific steps in this process.

6.1.5 Study Development

6.1.5.1 Proposal Process

Anyone may submit a proposal to use the CIBMTR Research Database at any time. Each fall, the CIBMTR extends a formal invitation to center clinicians and basic scientists to submit proposals. This communication includes website links to proposal submission instructions, including those that require Research Sample Repository specimens. To guarantee consideration by the Working Committees at the TCT Meetings, proposals must be submitted a minimum of two months before the meetings, generally no later than November 15. Scientific Directors, in consultation with the appropriate coordinating MS-level Statistician, may accept proposals received after this date if preliminary assessment is possible prior to the meeting of the relevant Working Committee.

Before submitting a proposal, investigators are encouraged to view CIBMTR *data collection forms* to verify that critical data are available for their proposed study. Depending on the time-period considered in the proposed study, PIs should also review previous versions of forms. Investigators should also review the current online listing of studies in progress to avoid proposals for ideas / studies previously accepted. Lastly, a preliminary discussion with Working Committee leadership can be helpful in determining the feasibility of studies and the level of enthusiasm for the research idea.

On occasion, studies are proposed in collaboration with other registries, cord blood banks, or professional transplant groups / societies. During the proposal process, details must be clarified related to merging of data and who will provide analytic support as these matters affect assignment of statistical resource hours, the study plan, and projected timeline.

When a proposal is first received, the investigator is notified of receipt, and a proposal number is assigned for tracking purposes. The proposal is then forwarded to the appropriate Scientific Director and MS-level Statistician, who review the proposal for feasibility with CIBMTR data and potential conflict with active studies. The MS-level Statistician then forwards the proposal to the Chairs for discussion. In cases of conflict or feasibility issues, the Scientific Director or Committee Chair communicates with the PI regarding modifying or withdrawing the proposal. When such determinations are not straightforward, the proposal may be discussed at a Coordinating Center weekly statistical meeting, as noted above in **Section 6.1.4**. Most proposals are approved for presentation at the annual Working Committee meeting. However, Chairs may consider certain proposals for expedited approval and implementation after discussion with the Senior Scientific Director for Research Operations. Such expedited approval requires delaying progress on other studies and is considered only for proposals with potential for high impact or time-sensitive funding opportunities.

Prior to presentation of a proposal at the annual Working Committee meeting, the MS-level Statistician prepares a table describing the study population, as specified within the proposal, to allow assessment of potential sample size and feasibility. This may be presented at the Coordinating Center weekly statistical meeting (prior to the annual meeting) if the Working Committee Leadership request additional Coordinating Center input. Such discussions may

result in suggestions to the PI for amending the proposal prior to presentation. These suggestions are communicated by the Working Committee Chair or Scientific Director.

The Working Committee membership in attendance at the TCT Meetings helps prioritize the proposals and decide (by written ballot ranking) the order of interest and scientific value (e.g., novelty of idea, clinical relevance, and the chance of it being published in a high-quality journal). Working Committee Chairs, charged with final decisions, consider this input in preparing an agenda for the committee's activities for the next academic year. The primary approval criteria for evaluating proposals are scientific merit and feasibility. When deciding among proposals of similar merit, preference is given to those proposed by investigators from CRF-submitting centers in good standing. (See **Chapter 3** for more information).

The CIBMTR encourages PIs who submit proposals to attend the TCT Meetings and personally present their ideas to the Working Committee membership. This enables the investigator to answer committee membership questions, convey enthusiasm for the proposal, and explain its clinical relevance. Investigators are notified within approximately one month of the results of the deliberations of the Working Committee and after final Advisory Committee approval of the complete CIBMTR research agenda. If proposals are rejected, the PI is informed by the Working Committee Chair(s) or Scientific Director of the fundamental issues resulting in the rejection. If a proposal is accepted and assigned a study number, a PI (typically the individual who proposed the original concept) is assigned and informed of his / her responsibilities throughout the duration of the study process.

If a proposal addresses the same scientific question as an ongoing study, the proposer may be asked to join the Writing Committee of that study, if it is in an early stage. Additionally, the scope of an ongoing study may be amended to accommodate a different population (e.g., pediatric vs. adult) suggested by a new proposal.

PI responsibilities are best understood when familiar with the CIBMTR study process. Guidelines describing these processes and instructions for preparing a protocol are provided to each PI upon study acceptance (**Appendix B**). PIs are asked to read the guidelines and also:

- Read the CIBMTR Guidelines for Acquiring PMCID Numbers (**Appendix C**);
- Assist the Working Committee Chairs and Coordinating Center staff to develop a reasonable timeline for study completion;
- Prepare a first draft study protocol by the date specified by the Coordinating Center upon proposal acceptance;
- Prepare the Final Study Protocol (having considered all Writing Committee comments) within 30 days of distribution date to full Working Committee (the CIBMTR Coordinating Center sends deadline reminders 14 days in advance);
- Participate actively in teleconferences and meetings (e.g., weekly Statistical Staff meetings upon invitation);
- Participate actively in data file preparation and analyses;
- Prepare study materials, as necessary, for submission for meeting presentation;
- Prepare a first draft of the manuscript within 30 days of receiving the final study results;

- Prepare any subsequent manuscript draft within 30 days of prior distribution to Writing Committee;
- Collate and prepare memos addressing comments of Writing Committee members at protocol, analyses, and manuscript stages;
- Collaborate with the CIBMTR Coordinating Center to submit the manuscript;
- Address comments from reviewers, including input from CIBMTR Scientific Directors, Statisticians, and other co-authors;
- Respond to editorial questions and approve galley proofs;
- Upon proposal acceptance, return a signed, study-specific "Letter of Commitment" (**Appendix D1** or **D2**) by the specified deadline. The PI (and co-PIs if applicable) is asked to sign this letter, agreeing to fulfill responsibilities as described. If the PI is unable to meet these responsibilities as outlined within a reasonable time frame, Working Committee leadership, or a member of the Coordinating Center staff, may reassign the Study PI role to another individual.

The Study PI, in collaboration with the Coordinating Center, ensures that the specified deadlines at each phase of the study are met. Time to produce the data sets is dependent on the following: a) How much accrual is needed to have an adequate sample; b) quality of data, such as volume of missing data for key variables; and, c) overall follow-up of patients resulting in unanticipated, but reasonable, delays in the study. Occasionally studies are raised to a higher priority or studies do not progress as planned. In these cases, resources may be reallocated as needed. Every attempt is made to maximize productivity with limited resources. Generally, the CIBMTR expects studies to be completed within 18-24 months. Delayed studies are monitored closely, and if necessary, actions are taken to facilitate speedy completion or removal.

The CIBMTR Review and Approval of Working Committee Studies SOP (SOP-0067) details the specific steps in this process.

6.1.5.2 Assignment of the PI

After acceptance by the Working Committee, each study is assigned a study number identifying it by Working Committee abbreviation and year of acceptance. The person proposing the study generally becomes the study PI. An exception to this policy may be made if the person proposing a study has only a trivial proportion of the cases to be studied and a member of a center with a large proportion of the patients also requests to lead the study. These situations are uncommon and adjudicated by the Working Committee Chairs, Senior Scientific Director for Research Operations, and Chief Scientific Director. Investigators from centers contributing a high proportion of the data are given preference. Most disputes are resolved by appointing co-PIs with agreement about authorship order made in advance (see **Chapters 3 and 4**).

6.1.5.3 Protocol Development

The first step in the implementation of a study is development of a study protocol. The study protocol is an essential tool that clarifies the study objectives to Working / Writing Committee participants, and it guides MS-level Statisticians and Statistical Directors to ensure that these objectives will be met by the analyses conducted at the Coordinating Center. When notified of acceptance, each PI is asked to submit a draft protocol by a date specified by the Coordinating

Center in the Letter of Commitment (**Appendix D1** or **D2**). A guideline for preparing the draft is provided. The draft must include:

- Research Hypothesis: Scientific assumption that is the basis for the study;
- Objectives: Specific aims that will be achieved by the proposed analysis;
- Scientific Justification: Summary of the study rationale that conveys the study's importance;
- Study Population: Definition of selection criteria;
- Outcomes: Clear definition of study outcomes, including any relevant time-points;
- Variables to be Analyzed: Listing of explanatory variables, based on biological principles, available in the Research Database and proposed format / categories for analysis;
- Data Collection: Specification of supplemental data required and a plan for data collection;
- Study Design: Statistical approach to achieving each objective (this will be refined with support of Coordinating Center Statisticians);
- References.

Once received by the Coordinating Center, this draft protocol is further refined in collaboration with the Working Committee Statistician, Statistical Director, and Scientific Director. A table including a preliminary description of the proposed population is added, and the draft protocol is presented at a Coordinating Center weekly statistical meeting.

6.1.5.4 Establishing a Writing Committee

Writing Committees are formed early to supervise study progress. Interested investigators are invited to participate when, after approval by CIBMTR's Scientific and Statistical group, the final draft protocol is distributed by the Coordinating Center to all Working Committee members and center directors who contributed data for substantial numbers of patients meeting the eligibility criteria for the study. Numbers of patients from each contributing center are included in the materials prepared earlier by Statisticians to facilitate discussion about center participation during proposal / protocol development, as noted below.

After distribution of the invitation soliciting Writing Committee membership, Working Committee Chairs and Scientific Directors review the Writing Committee membership and the study population. If a center that is among the five centers with the largest numbers of cases in the study or a center that contributes 10% or more of the cases is not represented on the Writing Committee, an additional memo is sent to the center director to determine whether the center wishes to designate a representative for the Writing Committee.

To assure co-authorship (**Chapter 3**), members of the Writing Committee must make timely and substantive contributions to study design, data analysis, interpretation of results, and preparation of the typescript for publication. The CIBMTR expects all Writing Committee members to provide substantive input and timely commentary during subsequent developmental stages of the study. Writing Committee members who do not fulfill this requirement are expected to withdraw as a co-author or, alternatively, the PI may remove their names.

6.1.5.5 Supplemental Forms / Data Collection

If the study requires supplemental data collection (i.e., data not collected on CIBMTR report forms), development of a supplemental form may be required. Coordinating Center staff design supplemental forms in collaboration with the PI and Working Committee leadership. All but the simplest forms must be piloted before implementation, and time must be allowed for the appropriate data entry screens to be added to FormsNet. In general, this step tends to delay the study timeline by one year and typically results in an increase in the number of statistical hours required for study completion. For these reasons, studies requiring this step are not encouraged.

6.1.5.6 Data File Preparation

The objective of study file preparation is to have a data file of eligible subjects who are consecutively treated at participating centers with adequate follow-up, minimal missing data items, and in large enough numbers to give the analysis sufficient statistical power to meet the stated study objectives. This process involves a series of steps on the part of the MS-level Statistician, sometimes working together with a Clinical Research Coordinator, to ensure data quality. It often involves consultation with the PI as well as Scientific Directors and Statisticians at the Coordinating Center. These steps include:

- Finalizing selection criteria;
- Determining the adequacy of follow-up and taking steps to obtain additional follow-up information if necessary;
- Evaluating the extent and nature of missing values and their potential effect on the study and takings steps to obtain missing data if necessary and feasible;
- Identifying data discrepancy / outliers and reconciling these by examining data collection forms or communicating with centers;
- Determining appropriate groups for continuous and categorical variables, if not already specified in the protocol;
- Describing the included and excluded patients so that the investigators can determine whether the final study population is representative of the target population (unbiased sample).

6.1.5.7 Analysis

Analysis proceeds in several phases. The first analysis generally includes a detailed description of the patient population and univariate analyses of study endpoints. Sometimes a preliminary multivariate analysis is also performed. These data are distributed to Writing Committee members requesting their suggestions and comments. An iterative process then ensues. The PI works with Working Committee leadership to discuss and address comments raised by the Writing Committee. Revised analyses, with a description of steps taken to address comments, are then distributed to the Writing Committee. It is the PI's responsibility to draft this memo with input from the Working Committee leadership. If additional substantive comments are made by the Writing Committee, the process is repeated until a final analysis is available. This final analysis serves as the basis for the manuscript.

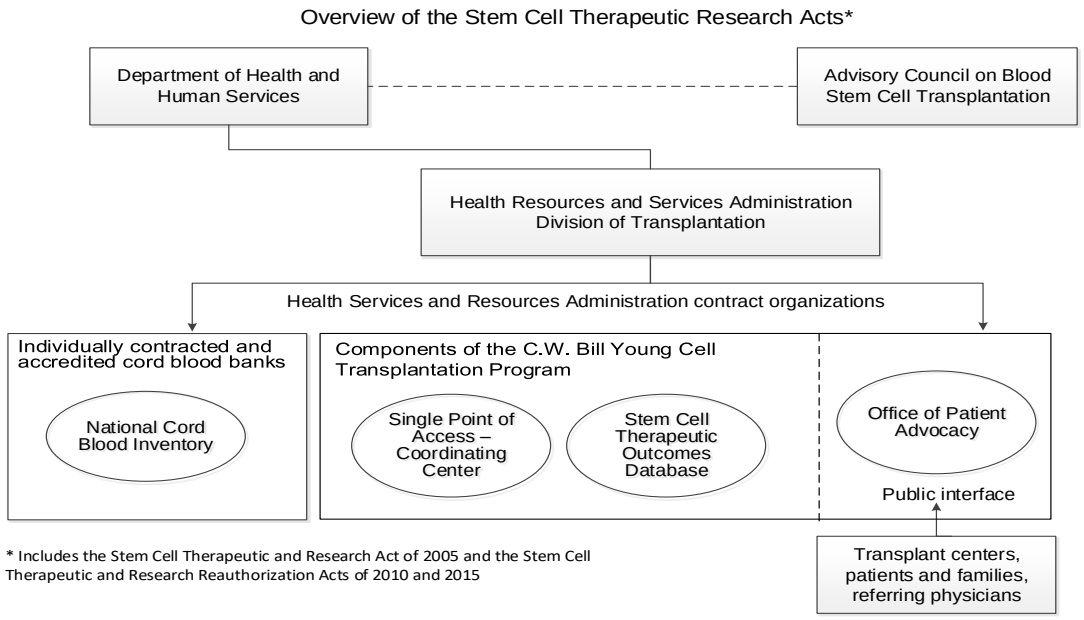
6.1.5.8 Manuscript Preparation and Submission

See **Chapter 4**.

6.2 STEM CELL THERAPEUTIC OUTCOMES DATABASE

In 2006, the CIBMTR was awarded a contract from HRSA to create and manage the SCTOD. The SCTOD is a national registry for allogeneic transplant information. It is a component of the C.W. Bill Young Cell Transplantation Program (the Program), which was established by the Stem Cell Therapeutic and Research Act of 2005 (passed by Congress and signed by President Bush in December 2005 as Public Law 109-129) and reauthorized by the Stem Cell Therapeutic and Research Reauthorization Act of 2010, Public Law 111-264 (signed by President Obama in October 2010) and Stem Cell Therapeutic and Research Reauthorization Act of 2015, Public Law 114-104 (signed by President Obama in December 2015). The CIBMTR renewed the contract in 2012 and 2017. **Figure 6.1** shows an overview of the Stem Cell Acts.

Figure 6.1: Overview of the Stem Cell Therapeutic and Research Acts



The Program was designed to help patients who need a transplant from an unrelated adult marrow, peripheral blood stem cell, or cord blood unit donor. Its goal is to increase the numbers of unrelated marrow donors and available cord blood units, expand research to improve patient outcomes, and provide information about HCT to patients and their family, health care professionals, and the public. There are three components of the Program, each with its own HRSA contract:

- Single Point of Access - Coordinating Center (Program contractor is the NMDP/Be The Match);
- Office of Patient Advocacy (Program contractor is NMDP/Be The Match; the NMDP/Be The Match Patient Advocacy and Navigation Department serves in this role);
- SCTOD (Program contractor is the CIBMTR).

The three components of the Program, including the SCTOD, work together to:

- Operate a system for identifying, matching, and facilitating distribution of blood stem cells;
- Allow transplant physicians, health care professionals, and patients to search online for available cord blood units and adult donors;
- Support studies, demonstrations, and outreach projects for the purpose of increasing cord blood donation and volunteer adult donors, to ensure genetic diversity;
- Carry out informational and educational activities to increase cord blood donation, promote cord blood units as a transplant option, and increase the number of adult donors.

The CIBMTR accomplishes Program requirements directly or through sub-contracts. The CIBMTR subcontracts with NMDP/Be The Match to provide some services, including information technology, maintenance of the related donor-recipient Research Sample Repository (**Chapter 7**), auditing, and continuous process improvement support for data management and quality assurance (**Chapter 11**).

In addition to the three components of the Program, HRSA has awarded contracts to individual cord blood banks for the National Cord Blood Inventory, which collects, stores, and provides high-quality umbilical cord blood units to patients and, in some cases, to researchers. The Advisory Council on Blood Stem Cell Transplantation advises the Secretary of the US Department of Health and Human Services and the Administrator of the HRSA on the activities of the C.W. Bill Young Cell Transplantation Program and the National Cord Blood Inventory Program. For more information, see the *HRSA Program* website.

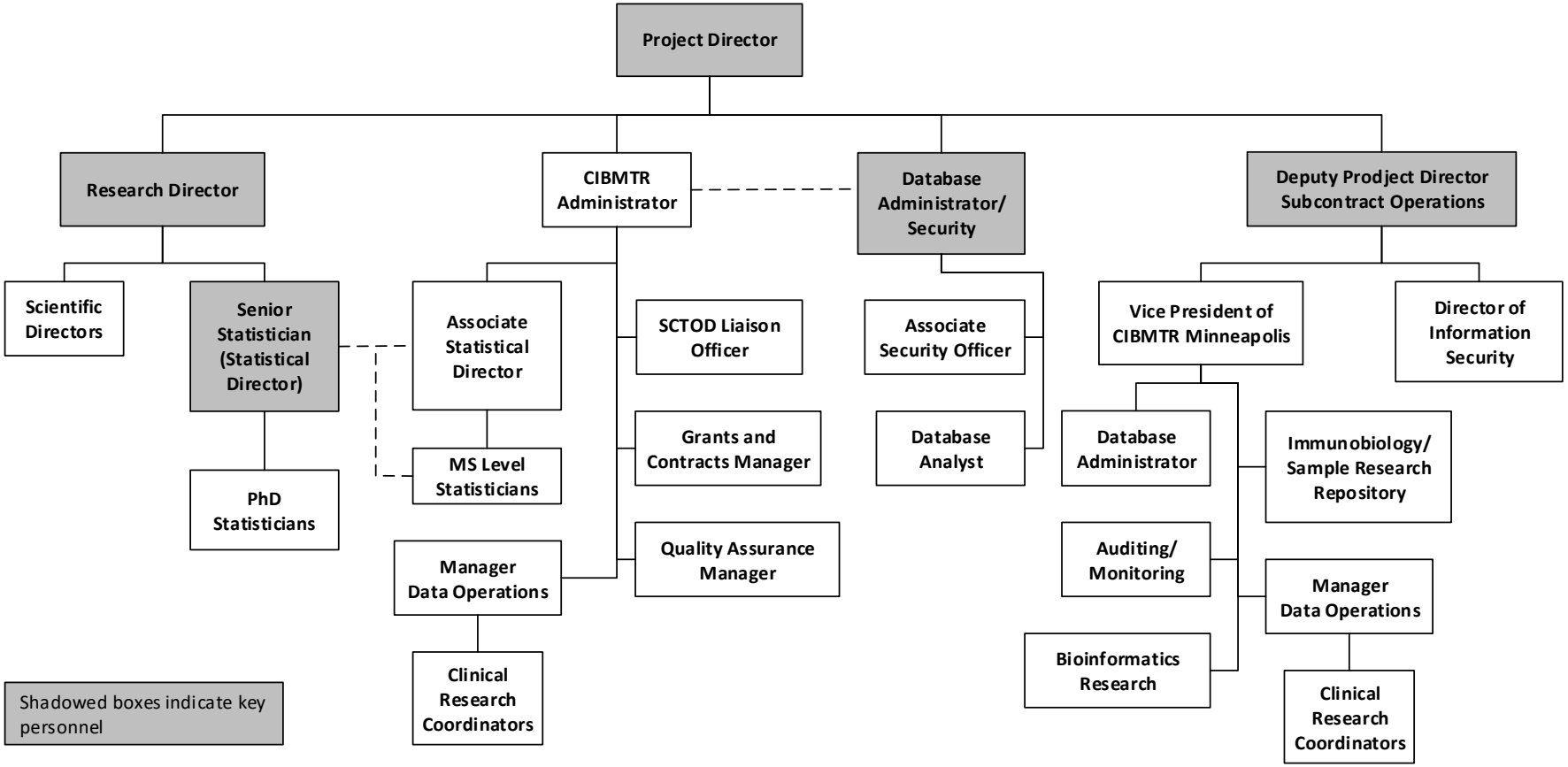
6.2.1 SCTOD Oversight

CIBMTR staff members oversee the administration of the SCTOD. **Figure 6.2** shows the organizational structure of the CIBMTR relevant to the SCTOD.

Key staff members include:

- **Project Director (CIBMTR Senior Scientific Director).** The Project Director has overall responsibility for successful execution of the contract. The person filling this role monitors progress of data collection, research, business and communications activities, assisted by the Research Director, Deputy Project Director Subcontract Operations, Senior Statistician, Liaison Officer, and Contracts and Administration Manager. He / she works closely with CIBMTR Scientific Directors and Medical Consultants and is the primary point of contact for the SCTOD.
- **Research Director (CIBMTR Chief Scientific Director).** The SCTOD Research Director oversees CIBMTR technical and scientific activities with input from the Advisory and Working Committees. The person filling this role reports to the Project Director for oversight of the work of the SCTOD and has primary responsibility for preparing and supervising its research agenda.

Figure 6.2: SCTOD Organizational Structure



- **Deputy Project Director Subcontract Operations (Associate Scientific Director).** The Deputy Project Director Subcontract Operations over sees CIBMTR technical and scientific activities of the subcontract scope of work. The person filling this role reports to the Project Director for oversight of the subcontract work of the SCTOD.
- **Senior Statistician (CIBMTR Statistical Director).** The Senior Statistician reports to the Research Director for all contractual matters related to statistical analyses. The person filling this role has primary responsibility for ensuring that the methodology used for analytic and research tasks of this contract is sound, and for developing innovative approaches to analytic issues.
- **Database Administrator / Security Officer (CIBMTR IT Director - MKE CIBMTR Information System Security Officer).** The Database Administrator / CIBMTR Information System Security Officer reports to the Project Director and has primary responsibility for ensuring the integrity and security of the Research Database to comply with federal security regulations. He / she also develops data query tools, disseminates data to Program components and centers, provides datasets to the Statistical team for use in CIBMTR analyses, and assists in development of systems to receive data from other registries or data sources. This individual collaborates with the Information System Security Officer in Minneapolis.

Additional SCTOD personnel (with CIBMTR titles in parentheses, if different) includes:

- **Administrator (Executive Director CIBMTR Milwaukee).** The Executive Director in Milwaukee reports to CIBMTR Chief Scientific Director and, works with the CIBMTR Vice President for Research Operations in Minneapolis, supervises the IT, Statistics, Data and Business Operations functional areas as well as data collection, training programs, quality control and audit activities to ensure the availability of high-quality data.
- **Liaison Officer (Program Manager for SCTOD).** The Liaison Officer reports to the Project Director via the Executive Director, Milwaukee. This individual coordinates communications with HRSA and among the CIBMTR, NMDP/Be The Match, and other Program contractors. The Liaison Officer also tracks and prepares deliverables to ensure deadlines are identified and met; coordinates and schedules meetings and action items; and provides administrative support to the Project Director.
- **Contracts and Administration Manager (Financial Associate).** The Contracts and Administration Manager reports to the Project Director via the Executive Director, Milwaukee and is responsible for ensuring that all required financial and administrative reports for the contract and NMDP/Be The Match subcontract are completed in a timely manner. The Medical College of Wisconsin Grants and Contracts Office and Office of Sponsored Programs assist with administrative, contractual, and reporting requirements.
- **Associate Statistical Directors.** The two Associate Statistical Directors report to the Senior Statistician, Executive Director, and Project and Research Directors. They are responsible for supervising, training, and coordinating MS-level Statisticians and monitoring Working Committee progress. They also analyze outcomes data, help

develop data collection tools, and participate in design and generation of required reports.

- **PhD-level Statisticians (CIBMTR Statistical Directors).** PhD-level Statisticians report directly to the Senior Statistician and provide statistical direction for SCTOD-related studies.
- **MS-level Statisticians.** MS-level Statisticians report to the Project Director, Research Director, Executive Director, and Senior Statistician. They perform analyses of Program data, support Working Committee research under the direction of the Chief Scientific and Statistical Director, coordinate Working Committee activities including ensuring communication with Working Committee Chairs and other members, and monitor Working Committee studies.
- **Scientific Directors.** Scientific Directors report to the Research Director. They provide unique clinical perspective as HCT physicians with MS degrees in biostatistics, epidemiology, and / or clinical research and immunology. They communicate with investigators seeking to use Program data, serve as the primary liaison with Working Committee Chairs, and provide guidance to statistical personnel. They consult on the design of data collection forms / systems, data elements, and studies. Scientific Directors also supervise scientific aspects of Working Committee studies, evaluate proposals that use the SCTOD, provide medical input for data collection issues, and ensure that studies involving the SCTOD are efficiently completed with scientific rigor.
- **Vice President of Data Operations (CIBMTR Vice President).** The Vice President reports to the Deputy Project Director Subcontract Operations. This individual, working with the Executive Director supervises (through Managers of Data Operations) data collection, training programs, and quality-control and center audit activities to ensure availability of high-quality research data. Assistance is provided in day-to-day SCTOD operations, ensuring activities are in compliance with applicable federal privacy and human subjects regulations.
- **Database Administrator (CIBMTR Minneapolis Director of IT).** The Database Administrator reports to the Vice President of Data Operations. The person filling this role leads development of FormsNet and A Growable Network Information System (AGNIS) (**Chapter 14**). He / She partners with the Database Administrator / Security Officer in Milwaukee to oversee SCTOD functions and activities.
- **Immunobiology / Research Repository Director (Scientific Director).** This Director reports to the Deputy Director Subcontract Operations and provides Repository management services through NMDP/Be The Match. This individual oversees activities related to development, management, and maintenance of the Research Sample Repository including integration with the Clinical Database. He / She partners with the Associate Statistical Director in Milwaukee to supervise MS-level Statisticians.

6.2.1.1 Policies and Technical Direction of the SCTOD

The CIBMTR Advisory Committee functions as a board of directors for the SCTOD (**Section 2.2.2**). They establish policies and technical direction for the CIBMTR, including the SCTOD. It is comprised of experts in the stem cell transplantation field and two representatives of the Division of Transplantation of HRSA that serve as ex officio members, as does one

representative from the Department of Defense Marrow Donor Recruitment and Research Program of the Department of the Navy. This assures government representatives are aware of all proposed policy changes and have adequate time to review significant policies impacting the Program.

If a proposed policy change is recognized to be significant and have conflict with policies of the Program, the CIBMTR will provide an assessment of the policy impact along with recommendations to the HRSA Contract Officer Representative at least 30 days in advance of CIBMTR Advisory Committee notification.

6.2.2 Key Activities

The SCTOD contract requirements are to:

- Collect HCT outcomes data on:
  - All allogeneic HCTs performed in the US using related or unrelated donors;
  - All allogeneic HCTs worldwide that use grafts procured through the Program;
  - Clinical applications other than hematopoietic cell recovery.
- Use the data collected for the SCTOD to evaluate the performance of centers.
- Provide certain SCTOD data to the public.
- Collect a basic set of data for analyses of Program use, center-specific outcomes, donor registry, cord blood inventory size, and patient access to HCT.
- Establish and maintain a related donor-recipient Research Sample Repository.

Basic information is collected for all allogeneic and autologous HCTs on the TED form (**Chapter 11**). TED forms were initially developed by the CIBMTR in collaboration with international partners to capture the most essential data for understanding the transplantation procedure and its outcomes. The TED forms were also designed to meet SCTOD requirements, including collection of data considered important for center-specific outcome reporting. The TED forms require Office of Management and Budget (OMB) approval every three years or as changes are made. Form review occurs at least annually and incorporates a broad group of expert stakeholders, representing an international consensus on a basic data set to be collected for all HCT recipients.

FormsNet, a web-based application designed specifically for the SCTOD, provides a single platform for US and non-US centers to submit federally required outcomes data to the CIBMTR. FormsNet allows bi-directional communication between the CIBMTR and centers. For more information, see **Chapter 14**.

6.2.2.1 Completing SCTOD Contract Performance Requirements

The SCTOD contract includes a Performance Work Statement with nine performance requirements, which are further categorized into specific deliverables to be submitted to HRSA. These are updated with each five-year contract renewal, and some may already be complete in fulfillment of the current contract. The following performance requirements are associated as numbered and named below with the contract effective 9/27/17-9/26/22:

3.1 Fulfill Contract Administration Requirements

- 3.1.1 Attend Initial/Kick-off Meetings

- 3.1.2 Attend Quarterly COR Meetings
- 3.1.3 Attend Special COR Meetings
- 3.1.4 Conduct Briefings
- 3.1.5 Establish Policy and Technical Direction of the SCTOD
- 3.1.6 Establish the Cord Blood Data Policy

3.2 Collect Stem Cell Therapeutic Outcome Data

- 3.2.1 Define and Update Common Data Elements to be Collected
- 3.2.2 Submit Materials for Clearances
- 3.2.3 Collect and Maintain Outcomes Data
- 3.2.4 Collect and Maintain Data Use of Adult Stem Cells and Birthing Tissues to Develop New Types of Therapies
- 3.2.5 Evaluate Data Collection Process and Assess Gaps in Data
- 3.2.6 Develop a Data Validation and Verification Plan
- 3.2.7 Implement process to Maintain Historical Datasets and Programming Codes

3.3 Provide Analytical Support

- 3.3.1 Support Planning, Implementation, Evaluation of OPA Activities
- 3.3.2 Support Planning, Implementation, Evaluation of SPA-CC Activities
- 3.3.3 Provide Analytic Support to HRSA

3.4 Disseminate Data

- 3.4.1 Disseminate Data Sets and Summaries to the Public
- 3.4.2 Allow Participating Organizations to Obtain their Organization Data
- 3.4.3 Establish Policy for Data Release
- 3.4.4 Provide Quarterly Download of SCTOD Data
- 3.4.5 Create Standard Analysis Files (SAFs)
- 3.4.6 Respond to Non-Federal Government Data Requests

3.5 Report on Research

- 3.5.1 Report on Research Priorities in the Field of Stem Cell Transplantation and Cellular Therapy
- 3.5.2 Establish and Maintain One or More Sample Repositories for Research

3.6 Provide Special Reports

- 3.6.1 Report on the Current State of Quality of Life for Transplant Recipients
- 3.6.2 Compare Treatment Options and Outcomes
- 3.6.3 Report on Actions to Improve Patient Late-Effects

3.7 Submit Reports

- 3.7.1 Submit Monthly Progress Reports
- 3.7.2 Provide a Quarterly SCTOD Function Report
- 3.7.3 Submit Annual End-of-Performance-Period Report
- 3.7.4 Submit Annual Statistical Report on SCTOD Activities

- 3.7.5 Develop a Report on Survival Rates for Each Transplant Center in the US
- 3.7.6 Dissemination of Transplant Center Survival Rates Reports
- 3.7.7 Provide Cord Blood Bank Reports

3.8 Provide HRSA OIT Requirements

- 3.8.1 Manage Federal Records
- 3.8.2 Complete Records Management Training
- 3.8.4 Ensure Section 508 Compliance

3.9 Perform Optional Tasks

- 3.9.1 Submit Transition Plan from Predecessor
- 3.9.2 Transition to Successor Contractor (if applicable)

4.0 Security and Privacy Requirements Annex

- Incident Response

6.2.2.2 Conducting Specialized Research

In fulfillment of its SCTOD contract deliverables, as discussed above, the CIBMTR conducts specialized research in the following areas.

- **Emerging Clinical Applications.** The CIBMTR maintains a system for collecting and analyzing outcomes information when cells derived from bone marrow, peripheral blood, or umbilical cord blood are used for clinical applications other than HCT (e.g., for cardiac or central nervous system regeneration). This system identifies key data to be collected as well as potential data sources (blood banks and collection centers, cord blood banks, processing centers, clinical centers, and the Food and Drug Administration).

  Since January 2009, cellular therapy registration data have been collected on CIBMTR Form 4000 in FormsNet. Subsequently, CIBMTR has developed a Cellular Therapy Registry and implemented a full suite of longitudinal data collection forms focused on non-HCT uses of cellular therapies. CIBMTR has hosted annual meetings since 2015 to generate recommendations from clinical, research, registry, industry, and regulatory stakeholders on the necessary data elements to be captured and indications to be supported by the Cellular Therapy Registry. The resulting CTED forms were released in Summer 2016, with revised versions released in July 2017 and January 2018. Although efforts initially focused on cellular immunotherapy for cancer, efforts are also focused on use of cell therapy for regenerative medicine. CTED forms have been developed in collaboration with the European Society for Blood and Marrow Transplantation (EBMT) and other international registries. The Cellular Therapy Registry will help inform HRSA regarding decisions to include such new therapies within the purview of the Program.
- **Inventory and Adult Donor Model Analyses.** The SCTOD requires an analysis of the ideal size and composition of both the NCBI and the Program's adult donor registry. The analysis must include an estimate of the effect of different scenarios of Program growth on the probability that a patient in each of several racial / ethnicity categories would find a specified number of potentially matched cord blood units / adult donors. The

approach and specific methodologies were developed with NMDP/Be The Match, the CIBMTR, external modeling experts, the Single Point of Access Coordinating Center, the Office of Patient Advocacy, and HRSA project staff.

- **Center-Specific Survival Analyses.** Though NMDP/Be The Match has been analyzing transplant center outcomes for unrelated donor HCTs since 1994, these analyses are now under the purview of the CIBMTR as required by the contract, and they now include data on related donor HCTs. Reports provide one-year survival statistics for all US centers doing allogeneic HCT, both related (since 2008) and unrelated, using a three-year rolling window. The reports compare observed and expected survival rates with a 95% confidence interval. Because centers vary considerably in the risk level of the cases they treat, the CIBMTR developed a statistical model to adjust for risk factors known or suspected to influence outcomes. Reports are submitted to HRSA each year, and copies are distributed to center medical directors and payers. Results are published on the Be The Match *Transplant Center Search* webpage. These reports are useful for improving quality of HCT and informing the public about them.

  Since 2008, the CIBMTR has conducted biennial forums to discuss and develop plans to conduct these center-specific survival analyses with center representatives and experts in outcomes reporting and statistical analysis as well as patient and payer representatives. The last forum was held in September 2018. Recommendations generated during these forums are used to guide the center-specific survival analyses. These recommendations are distributed to US center medical directors and made available on the CIBMTR *Center Outcomes Forum* webpage.

6.3 CELLULAR THERAPY RESEARCH

In addition to receiving data on transplant patients, the CIBMTR receives data from more than 220 centers for patients who received cellular therapy. Indications for treatment include malignant hematologic disorders, suboptimal donor chimerism, prevention of disease relapse, neurologic disease, infection and GVHD treatment and prophylaxis, and other conditions. The CIBMTR receives cellular therapy data via a suite of CTED forms. These forms, harmonized with the European and Japanese registries, undergo real time review and revision.

6.3.1 Cellular Immunotherapy Data Resource

In September 2018, the CIBMTR received funding from the National Cancer Institute to serve as the CIDR to support the biomedical community and the IOTN. Both the IOTN and the CIDR are part of the Cancer Moonshot^{SM} initiative to accelerate cancer research to make more therapies available to more patients.

The goal of the CIDR is to provide the academic community, as well as relevant pharmaceutical partners, with an infrastructure for collection of high-quality data. Data include patient demographics, tumor characteristics, course of cancer treatment, cellular product manufacturing details, toxicity, and outcomes. The CIDR includes patients who received cellular immunotherapy for cancer as part of clinical trials as well as those treated with FDA-approved agents.

The CIDR relies on the CIBMTR cellular therapy registry infrastructure; however, it requires an independent governance structure to fulfill the objectives outlined in the program to interact

with the IOTN and other stakeholders. The CIDR Executive Committee (**Section 2.2.4**) was created to provide oversight to all activities related to this program.

The CIDR governance structure includes an Executive Committee that provides ongoing advice and counsel to the CIBMTR Coordinating Center relative to cellular therapy initiatives and the Cellular Immunotherapy for Cancer Working Committee, which oversees the utilization of data for research purposes. The CIBMTR re-organized its current scientific working committee structure in 2019 to create the Cellular Immunotherapy for Cancer Working Committee (**Section 6.1.1**). The CIBMTR Advisory Committee will share oversight responsibilities of this new Working Committee in order to provide the same performance metrics currently in place for all the Working Committees (**Section 6.1.2**).

6.3.2 Long-Term Follow-Up

The Food and Drug Administration (FDA) requires pharmaceutical companies that commercialize genetically engineered cellular therapies to follow recipients of these therapies for 15 years in order to evaluate their safety and efficacy. The CIBMTR supports this requirement and is currently partnered with several pharmaceutical companies to track these long-term outcome data.

6.3.3 Cellular Therapy Registry Forum

Since 2015, the CIBMTR has conducted annual forums to discuss and develop plans to create and enhance its cellular therapy registry. The last forum was held in October 2018. Recommendations generated during these forums are used to develop and improve the registry, including data collection and use. Examples of topics include CAR T toxicity grading criteria and reporting, cellular therapy center accreditation and data auditing, long-term follow-up infrastructure, considerations for capturing biospecimens in cellular therapy recipients, and updates from federal agencies.

6.3.4 Regenerative Medicine Outcomes Registry

Since 2017, the CIBMTR has hosted an annual regenerative medicine outcomes registry strategy meeting. The last meeting was held in September 2018 in association with Cord Blood Connect, an international conference hosted by the Cord Blood Association. Meetings focus not only on the CIBMTR's registry capabilities, including form development and collection of patient-reported outcomes, but also on determining disease priority and establishing working groups related to the regenerative medicine outcomes registry.

6.4 MEDICARE COVERAGE WITH EVIDENCE DEVELOPMENT (CED) STUDIES

Some Americans, such as many elderly individuals with myelodysplastic syndrome (MDS), were denied access to HCT therapy in the US due to lack of Medicare insurance coverage by the Centers for Medicare and Medicaid Services (CMS). To help secure Medicare coverage for these patients, the CIBMTR, NMDP/Be The Match, ASTCT, and other organizations partnered with CMS to launch CED studies. The CED approach allows CMS to provide coverage for procedures and to advocate for clinical studies that inform policy decisions. The CIBMTR is currently engaged in six CMS CED studies:

- Multiple Myeloma (17-CMS-MM): NCT#03127761
- Myelodysplastic Syndrome (10-CMS-MDS): NCT#01166009

- Myelodysplastic Syndrome (BMT CTN 1102): NCT#02016781
- Myelofibrosis (16-CMS-MF): NCT#02934477
- Sickle Cell Disease (17-CMS-SCD): NCT#01166009
- Sickle Cell Disease (BMT CTN 1503): NCT#02766465

6.5 PATIENT-REPORTED OUTCOMES

The CIBMTR implemented an electronic patient-reported outcomes (ePRO) system to support the collection of PRO data, to be linked with clinical data, in the registry. Instruments in the NIH Patient Reported Outcomes Measurement Information System (PROMIS*)* form the backbone of PRO data collected by the CIBMTR. The PROMIS measures capture patient-reported health status using a set of valid, generic, and adaptable assessment tools that cover a variety of domains related to physical, mental, and social health and functioning.

The CIBMTR may utilize multiple modes to collect PRO data, including electronic, pen-and-paper, or phone. When collected electronically, PROMIS measures are administered as computer adaptive testing (CAT) through the PROMIS Application Programming Interface (API) and are validated in multiple languages. CAT is a flexible, computer-driven measure that presents a respondent with items from an item bank. As a patient completes the initial question of a measure's item bank, the CAT algorithm selects only those next items that sharpen the estimate of the patient's score in the domain being measured, thus decreasing respondent burden as patients only see questions that are relevant to them.

PRO data are stored in the CIBMTR Integrated Data Warehouse (IDW), linked by CIBMTR Recipient ID (CRID) to clinical data. Data are then available to be shared with clinical trial investigators or to centers through existing CIBMTR data sharing portals and functionality, with the patient's permission (**Section 14.2.2**).

The CIBMTR's ePRO system is managed by staff of the Survey Research Group and CIBMTR Information Technology (CIT). This system integrates several applications:

- **Qualtrics®**. A cloud-based survey platform and the interface for building PRO surveys, generating unique survey links, and for patients to complete PRO surveys;
- **Salesforce®**. The client-relationship management system used by the CIBMTR for tracking PRO participants, time points, and activities;
- **Assessment Center Application Programming Interface (API)**. Delivers PROMIS measures using CAT functionality, and provides automated scoring of PROMIS measures;
- **FormsNet**. Pushes patient contact information and PRO enrollment and event dates to Salesforce to initiate PRO data collection time points;
- **IDW**. Pulls PRO data and scores from Qualtrics and links with clinical data.

The ePRO system is flexible and scalable, allowing additional measures at a variety of time points as relevant to individual clinical trials and long-term follow-up of patients.

CHAPTER 7: IMMUNOBIOLOGY RESEARCH

The CIBMTR Immunobiology Research Program was delineated as a distinct program in 2010. It leverages the NMDP/Be The Match investment in developing an unrelated donor-recipient specimen Research Sample Repository with the NIH's investment in the CIBMTR Research Database. These data are used to perform studies that link genetic and immunobiologic data with clinical phenotype data and outcomes.

The related donor-recipient specimen Research Sample Repository, an SCTOD contract requirement (**Chapter 6**), is a newer and unique opportunity to enhance immunobiologic research. Related donor and recipient samples are better matched than unrelated recipients for HLA, a measure of immunological compatibility, thus reducing the confounding effects of HLA disparity in clinical research. The related donor-recipient specimen Research Sample Repository facilitates a broader approach to studying transplant biology across the full spectrum of allogeneic HCT. The overall goal of immunobiology research is to facilitate studies that focus on:

- Improving outcomes after HCT and cellular therapy through a better understanding of the immune response pathways, HLA, and other genetic determinants of outcomes;
- Increasing the availability of unrelated donor HCT through a better understanding of donor and recipient genetic determinants;
- Understanding the role of HLA-matched or mismatched related and unrelated donor HCT compared to other available graft sources.

Examples of research supported by this program include:

- Genes and gene products of the major histocompatibility complex;
- Natural killer cell biology;
- Cytokines and other immune response determinants;
- Minor histocompatibility loci;
- Other immune regulatory genes and products (such as anti-HLA antibodies);
- Comparative studies that involve HLA-mismatched related donors or any unrelated donors;
- Advanced biostatistical methods to handle multi-dimensional, complex biologic and phenotypic data.

7.1 PROGRAM OVERSIGHT

The Immunobiology Research Program is overseen by the Immunobiology Working Committee leadership and the NMDP/Be the Match Histocompatibility Advisory Group. The Histocompatibility Advisory Group consists of appointed members and liaisons from the CIBMTR, NMDP/Be The Match, the American Society for Histocompatibility and Immunogenetics (ASHI), the NMDP/Be The Match Cord Blood Advisory Group, HRSA, and the C.W. Bill Young / Department of Defense Marrow Donor Program (Salute to Life). The Histocompatibility Advisory Group reviews and approves the use of donor-recipient specimens from the Research Sample Repository in CIBMTR studies and meets twice annually, in spring and fall, in person or via conference call.

Observational research studies that focus on immunobiology are conducted through the Immunobiology Working Committee using the clinical outcomes research process (**Chapter 6**).

The committee is unique in that it may have a Chair who is a PhD Scientist from a histocompatibility-focused laboratory background rather than an MD. In addition, it is assigned two Scientific Directors, ad hoc additional Statistical Directors, and MS-level Statisticians to accommodate the large number of studies that it conducts.

7.2 KEY ACTIVITIES

7.2.1 Clinical Outcomes Research Studies

To meet its research goals, the Immunobiology Working Committee collaborates with researchers in the clinical and basic sciences communities. Proposals are submitted via a formal mechanism for submission and review, and specific instructions can be found on the *CIBMTR How to Propose a Study* webpage.

Proposals are initially reviewed by the Chairs and Scientific Directors. Like all other Working Committees, studies are presented and discussed at the annual TCT Meetings, where members plan the scientific agenda and priorities for their committee. In addition, meritorious studies may be reviewed mid-cycle and approved if adequate support is available. For up-to-date information on committee structure, criteria that investigators must meet in order to submit research, information on proposals that require biologic samples, and contact numbers, refer to the *CIBMTR Sample Types and Inventory Summary* webpage or the *NMDP/Be The Match Research Resources* webpage.

Studies are approved based on scientific merit, originality, feasibility, and biostatistical considerations, including statistical power and the need for additional resources. Investigators with expertise in the basic biological sciences encompassing immunology, immunobiology, and human genetics are invited and encouraged to become actively involved in the Immunobiology Working Committee.

7.2.2 Research Sample Repository

The Research Sample Repository provides a unique resource to investigators for retrospective analysis of immune response determinants and transplant outcomes. NMDP/Be The Match has developed and actively maintains this Repository; sample types and an inventory summary are posted on the *CIBMTR Sample Types and Inventory Summary* webpage.

In return for access to the samples and data analysis support, investigators are required to submit the interpreted results of all assays performed on the samples to NMDP/Be The Match. This data submission requirement helps ensure that all sample testing yields information that is readily available to the research community for subsequent analyses, while also eliminating or reducing duplicate testing to conserve resources and sample inventory.

7.2.3 NMDP/Be The Match Research Activities

The CIBMTR, as the research program of NMDP/Be The Match, conducts research that supports the objectives of the Immunobiology Research Program. The Donor / Recipient Pair Project is a retrospective HLA typing project to characterize class I (HLA-A, B, and C) and class II (HLA-DRB, DQB1, and DPB1) alleles of stored donor / recipient paired samples from the Research Sample Repository. The *inventory summary* on the CIBMTR website includes details on the pairs typed through the project.

The data are stored in an NMDP/Be The Match-developed database and available to any researcher with a CIBMTR-approved study (**Chapter 6**) who wishes to analyze the impact of matching, as either the focus of or as a variable in, a research study. The allele-level data are also used to assess genetic diversity within the NMDP/Be The Match population. Genetic diversity analyses have focused on the evaluation of HLA haplotypes within the donor and recipient data set, made possible by the completeness of the loci characterized, the level of resolution achieved, and the high level of quality control. The statistical models developed for the project data were also applied to the NMDP/Be The Match HapLogic™ search algorithm, a donor search strategy developed by NMDP/Be The Match.

7.3 SIGNIFICANCE TO THE CIBMTR

The CIBMTR Immunobiology Research Program is significant to the CIBMTR in several ways:

- **Histocompatibility Expertise.** The Immunobiology Working Committee provides oversight for categorizing HLA matching data and other genetic factors for inclusion in CIBMTR research studies. The committee collaborates with the NMDP/Be The Match Histocompatibility Advisory Group to ensure the research priorities associated with histocompatibility in related and unrelated transplants (adult donor and umbilical cord blood) are addressed through the Immunobiology Research Program. The results of these research program studies are directly integrated into the histocompatibility matching guidelines promoted through the NMDP/Be The Match Histocompatibility Advisory Group.
- **Research Sample Repository**. A quality-controlled *Research Sample Repository*, linked to a well-developed prospective Research Database, is a unique and critical public resource. The Repository gives researchers a better understanding of allogeneic transplantation outcomes. It is the only resource accessible to the HCT research community for pre-transplant donor / recipient research samples collected from multiple institutions and tied to comprehensive clinical outcome data.
- **Statistical Expertise in Assessment of Genetic Polymorphisms / Diversity.** The Immunobiology Program employs a PhD Biostatistician with extensive expertise in the analysis of genetic polymorphisms in HCT (**Chapter 5**).

CHAPTER 8: CLINICAL TRIALS SUPPORT

The CIBMTR participates in and supports a variety of clinical trial activities to accomplish its mission of improving the success of HCT and cellular therapy. The CIBMTR supports investigators in planning these trials by providing resources, access to its Research Database, and statistical expertise. In addition to its clinical outcomes research (**Chapter 6**), the CIBMTR also supports two active clinical trials programs, the BMT CTN (**Section 8.1**) and the RCI BMT (**Section 8.2**).

8.1 BMT CTN

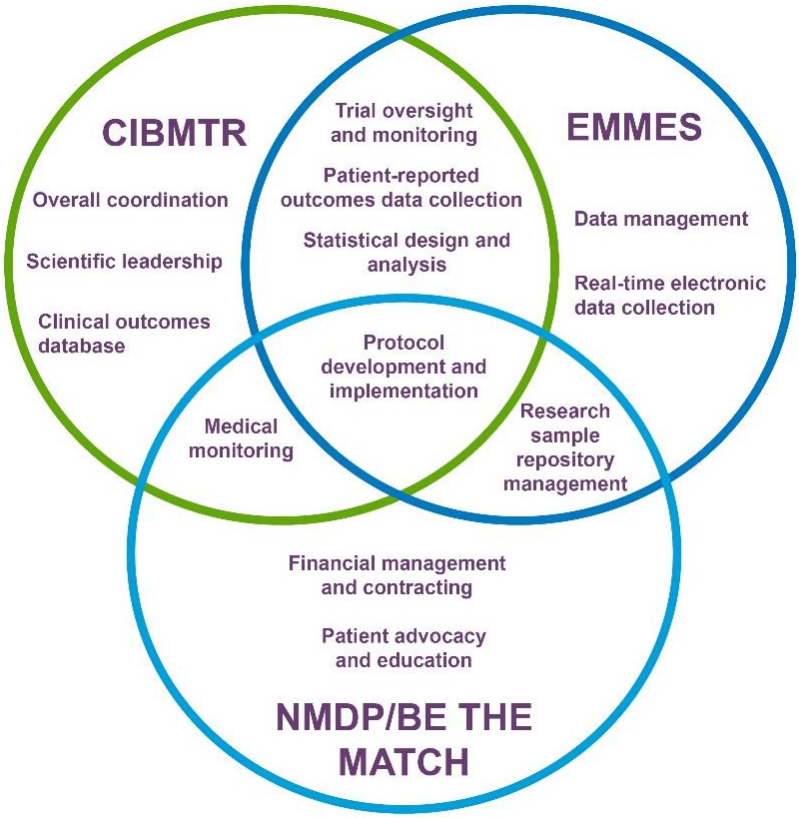
The BMT CTN, or the Network, was established in October 2001 to conduct large, multi-institutional Phase II and III trials addressing important issues in HCT and cellular therapy. The Network includes the BMT CTN DCC, 20 Core Clinical Centers, and about 80 Affiliate Centers.

8.1.1 BMT CTN DCC and the CIBMTR

The BMT CTN DCC coordinates all Network activities including operations, data management, communication, and statistical support. It is funded by a cooperative agreement from the NIH, with the NHLBI as the lead institute.

The CIBMTR shares administration of the DCC with NMDP/Be The Match and The Emmes Company, each with extensive research expertise. See **Appendix J** for a list of these shared responsibilities. The Chief Scientific Director of the CIBMTR serves as the DCC PI. **Figure 8.1** shows the key support roles of each of the three DCC organizations.

Figure 8.1: BMT CTN DCC



The DCC plays a key role in developing and facilitating study proposals and is responsible for statistical planning and collection of data from participating clinical centers. It manages all BMT CTN protocols, maintaining version control during development and after approval. It organizes, schedules, and prepares minutes and agendas for meetings and conference calls for the Steering Committee, Executive Committee, and others as requested. The DCC also maintains a private, password-protected website and a *public website* for the Network. For more information about the BMT CTN, including policies and procedures, see the annual BMT CTN Progress Report and Manual of Procedures on the *public website*.

8.1.2 Data Collection and Statistical Resources Provided by the CIBMTR to the BMT CTN

The CIBMTR Research Database is a key source of data for all BMT CTN studies, especially for accrual projections and statistical design. The CIBMTR makes data and statistical resources available to support the Network for the following activities:

- **Trial planning**. The CIBMTR's extensive Research Database of clinical information is used to assess the availability of appropriate patient populations for the specific eligibility criteria of each trial.
- **Data collection instruments**. The Network uses data collection forms developed by the CIBMTR. These include the TED forms used by most centers for submitting data and the CRFs used to collect more detailed information about transplants from a select group of centers (**Chapter 11**). Centers must provide CRFs for Network studies, even if they are required to provide only TED forms under the SCTOD (**Chapter 6**) guidelines.
- **Statistical consultation**. CIBMTR Statistical Staff provide design support and analytical review for BMT CTN protocols.
- **Trial interpretation**. CIBMTR data are used to evaluate the results of clinical trials by providing matched controls for patients treated in single and multi-institutional studies of transplant strategies, as required by the study protocol.

8.1.3 Data Submission

There are two ways to submit data to the BMT CTN:

- **AdvantageEDC℠ and Advantage eClinical℠ Systems.** These Web-based interactive data entry systems are housed at The Emmes Company. The Network uses their systems to record real-time study data. The DCC and centers can use these systems to generate lists of submitted, due, or delinquent forms for each patient and center. AdvantageEDC and Advantage eClinical forms include additional data fields that are not on the CIBMTR CRFs.
- **FormsNet℠**. This CIBMTR web-based system allows centers to electronically submit data to the CIBMTR using TED forms and CRFs. It was developed by the CIBMTR in fulfillment of SCTOD requirements for submission of outcomes data and also serves the Network by collecting longer term data such as quality of life and regimen-related toxicity.

8.1.4 Statistical Expertise

The CIBMTR and Emmes Statistical Staff are responsible for developing statistical designs, analytical methodology, and data analysis. CIBMTR and Emmes PhD Biostatisticians provide statistical review of clinical trial protocols and serve as expert resources for the protocols.

8.1.5 Accrual Planning, Monitoring, and Intervention

Adequate accrual is crucial to the success of the Network's clinical trials. The BMT CTN Project Manager, a CIBMTR staff member, assists in launching BMT CTN trials and develops, implements, and supports patient accrual strategies. The Project Manager works with Protocol Teams to assess accrual barriers prior to study launch and throughout the course of the trial and to develop protocol-specific accrual plans. This person also has ready access to CIBMTR databases, helps oversee all DCC activities, and coordinates key projects.

8.2 RCI BMT

The CIBMTR formed the RCI BMT to provide support for a wide array of clinical studies, including multi-center trials as well as survey and quality of life assessments. The RCI BMT, which conducts prospective research within the CIBMTR, provides researchers with infrastructure and expertise in clinical trial conduct and analysis. The RCI BMT's goal is to generate support for novel and innovative ideas, but it also supports Phase II / III studies and large survey and cohort studies.

Clinical trials services available through the RCI BMT include working with PIs to seek funding from a variety of sources, including government agencies, foundations, pharmaceutical companies, and private corporations; protocol development; regulatory support; study management; site management and monitoring; clinical data support; statistical support and analysis; and financial administration. PIs may also contract for specific services as needed, such as support with surveys, site selection and management, sample management, and more. The RCI BMT is led by the CIBMTR Chief Scientific Director, CIBMTR Associate Scientific Director, Senior Scientific Director for Data Operations, HSR Scientific Director, Vice President CIBMTR Minneapolis, Executive Director CIBMTR Milwaukee, and Director of Prospective Research. This group formulates and implements all policy decisions related to the program.

Leadership is supported by two teams within the CIBMTR: Clinical Studies Management and Survey Research. The staff includes Survey Research Supervisor, Clinical Project Managers, Data Managers, Clinical Research Specialists, Clinical Research Assistants, and Survey Research Associates. Staff members are responsible for the daily operation of prospective and observational studies conducted through RCI BMT. It is also supported by PhD-level statisticians from the CIBMTR who are faculty of the MCW Division of Biostatistics. Support for site monitoring activities are provided by the Audit / Monitoring team within the CIBMTR. The RCI BMT is supported by other NMDP/Be The Match departments, including Regulatory, Legal, Risk and Network Affairs Department, Contracts and Purchasing, and Finance. RCI BMT staff members work with the study Protocol Chair and protocol teams to:

- Collaborate with the PI to develop study protocols, procedures, reports, manuscripts;
- Prepare and submit applications and continuing reviews to the Data and Safety Monitoring Board (DSMB) and NMDP/Be The Match Institutional Review Board (IRB) (see **Chapter 12** and also **Section 8.2.4** in this chapter);
- Perform site selection, initiation, close-out, and interim monitoring visits;
- Coordinate contracts with centers;
- Identify and contract with suitable labs and repositories for study support;

- Coordinate communications among laboratories and repositories;
- Develop data collection forms and participate in development process management for the Clinical Database;
- Coordinate training and certification of center staff in standardized data collection and quality control procedures;
- Coordinate site activation, including site initiation training;
- Review data submitted on CRFs for completeness and accuracy;
- Monitor adverse events and participating center reporting;
- Communicate with participating centers regarding missing, delayed, incomplete, or erroneous data;
- Prepare periodic performance reports on participating centers;
- Maintain current participant rosters including RCI BMT roles and organizational affiliations;
- Coordinate meetings and conference calls, including site locations, travel arrangements, and call-in information;
- Coordinate communications among participating centers;
- Coordinate with other NMDP/Be The Match representatives to provide study support;
- Coordinate analysis of study data;
- Assist in preparing scientific reports for publication.

8.2.1 RCI BMT Trial Centers

All CIBMTR centers in the US are eligible to participate in trials, although not all trials are opened in all centers. Participation in specific protocols is determined by:

- Study design and requirements;
- Level of center commitment;
- Accrual targets;
- Competing protocols;
- Previous record of participation in multi-center trials.

8.2.2 Trial Selection and Progress Oversight

RCI BMT leadership reviews proposals and then submits them, as applicable, for additional review to the Clinical Trials Advisory Committee (**Chapter 2**), which evaluates and prioritizes them based on scientific merit, feasibility, and alignment with scientific agenda. This committee also reviews the progress of ongoing studies and makes recommendations where appropriate.

8.2.3 Data and Safety Monitoring Board

The RCI BMT has its own DSMB, which serves as an independent advisory body for studies not already reviewed by another DSMB mechanism. The primary function of the DSMB is ongoing assessment and monitoring of RCI BMT studies for their validity, safety, and efficacy. The DSMB includes an interdisciplinary membership with expertise in HCT and cellular therapy and the conduct of clinical trials. All applicable protocols must be reviewed and approved by the DSMB prior to submission to the NMDP IRB.

8.2.4 NMDP IRB

The NMDP IRB reviews all RCI BMT protocols as CIBMTR staff members are engaged in the trial research activities. It is an administrative body established to protect the rights and welfare of human subjects recruited to participate in NMDP/Be The Match and CIBMTR research activities. The IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction, as specified by both federal and state regulations and NMDP/Be The Match policies and procedures. The IRB must approve all RCI BMT protocols before they can be distributed to participating sites for their respective site IRB approvals. See **Chapter 12** for more NMDP IRB information.

8.2.5 Survey Research Group

The Survey Research Group is a team within the RCI BMT created to assist researchers in developing and conducting research involving questionnaires, direct subject interviews, and patient-reported outcomes. The group is responsible for collecting high quality, scientifically valid data from donors, patients, and their families. The Survey Research Group historically utilized standardized and semi-structured telephone interviews as well as self-administered questionnaires. The RCI BMT recently launched an ePRO system to support clinical trials, long term follow-up, and other research studies with patients and donors, utilizing PROMIS and other measures (**Section 6.5**).

8.2.6 Study Proposals

Investigators may submit study proposals to RCI BMT at any time by completing the proposal form, which is available upon request to the Director Prospective research or CIBMTR leadership.

8.2.7 Study Budget Management

Budgets are prepared and approved for each project. As noted above, all funding must include internal labor, travel, and protocol-specific expenses including items contracted to outside organizations such as laboratory, central pharmacy, or other products and services needed to accomplish the study objectives. Study budget management includes:

- **Study budget preparation and development.** RCI BMT staff members collaborate with the NMDP/Be The Match Finance Department, including Contracts and Purchasing, to prepare and develop budgets. This includes developing individual protocol budgets and coordinating funding for studies with external support.
- **Budget review process.** The final budget must be approved by the Director Prospective Research, CIBMTR Financial Officer, and Protocol Officer, as applicable .RCI BMT staff work with the NMDP/Be The Match Contracts and Finance Departments to create a Request for Proposals and contracts for centralized services, to finalize contributions, and to review the budget.
- **Expense tracking.** NMDP/Be The Match Contracts and Purchasing tracks and reconciles RCI BMT protocol-related funds, makes payments to suppliers, and reconciles all costs quarterly.

- **Budget revisions.** When significant changes are made to a protocol budget, either because of contributions or a change in costs, a new budget must be approved by the RCI BMT Budget Committee. Major increases in cost must be approved by the NMDP/Be The Match Chief Financial Officer and CIBMTR Chief Scientific Director.

8.2.8 Data Submission

There are three ways to submit data to RCI BMT:

- **RAVE platform.** This Web-based interactive data entry system is custom built for each study utilizing the Medidata cloud-based system. Rave allows real-time study data collection and immediate validation checks; query management and forms status functionality are built into each study.
- **FormsNet**. This CIBMTR Web-based system allows centers to electronically submit data to the CIBMTR using TED forms and CRFs. It was developed by the CIBMTR in fulfillment of SCTOD requirements for submission of outcomes data and also serves the RCI BMT for certain studies for collecting pre-treatment, survival data, and selected transplant and cellular therapy data.
- **ePRO.** This CIBMTR system utilizes NIH-funded PROMIS measures as its backbone and is administered as computer adaptive testing. The system is scalable, allowing additional measures to be collected, as identified by study needs.

8.2.9 Publications

RCI BMT leadership is responsible for developing and approving all publication and presentation policies. They also review all proposed publications and presentations to ensure protection of proprietary information and study participant confidentiality and to determine the public impact of publication and / or presentation of incomplete or premature results. No participating institution, protocol team, or other individual may present or publish individual findings from work performed on study protocols or work related to RCI BMT meetings and conference calls without approval of the RCI BMT leadership. This includes methodologic or position papers related to RCI BMT protocol development or operations.

See **Chapter 3** for more information about authorship guidelines and **Chapter 4** for manuscript submission policies.

8.3 OTHER PROSPECTIVE RESEARCH

In addition to the work of the BMT CTN and the RCI BMT, the CIBMTR facilitates:

- Unrelated donor research projects and interactions with donor centers to recruit and manage donor participation in the research;
- Survey research;
- HSR (**Chapter 9**).

These initiatives assist investigators with project planning, initiation, and conduct. When help is needed for a specific project, the CIBMTR:

- Facilitates communication among investigators and the large NMDP/Be The Match network of donor centers and cord blood banks, including recruiting and managing donor participation;

- Helps identify mechanisms for network participation in the research project;
- Assists investigators in identifying the necessary network resources;
- Helps investigators plan for use of these resources as they prepare their budgets;
- Ensures that a clear, feasible plan for network participation has been developed prior to submission of a research funding request (e.g., National Institutes of Health R01 funding);
- Assists with study initiation and conduct when funding is secured;
- Ensures that informed consent, altered collection procedures, additional blood or cell samples, or additional questionnaire requirements are completed efficiently.

CHAPTER 9: HEALTH SERVICES RESEARCH

HSR is the multi-disciplinary field of scientific investigation that studies how social factors, financial systems, organizational structures and processes, technology, and behavior affect treatment outcomes, quality, and cost. The HSR Program was established as a CIBMTR program in 2009. Its overall objective is to increase access to HCT and cellular therapy and improve patient outcomes through a well-balanced portfolio of health services and policy research that examines health services issues from a sociological perspective. Examples of research supported by this program include:

- Disparities in and barriers to access to HCT, including cultural and linguistic as well as socioeconomic factors;
- Survivorship and patient-reported outcomes such as quality of life and health behaviors;
- Treatment decision-making support, including for clinical practice and quality / value of care;
- Health economic and outcomes research, including healthcare utilization;
- Multiple research methods: Observational and prospective research designs, secondary data analysis, survey design and administration, data management and linkage, and qualitative and quantitative analyses.

9.1 PROGRAM OVERSIGHT

9.1.1 Program Leadership

The HSR Program is led by the Vice President and Senior Scientific Director, HSR. Oversight for the program is provided by the Senior Vice President of Research, NMDP/Be The Match, with additional scientific oversight provided by the CIBMTR Chief Scientific Director. The Scientific Director and Statistical Director of the CIBMTR Health Services and International Studies Working Committee also serve as ad hoc advisors (**Figure 1.1**).

9.1.2 Collaboration with the Health Services and International Studies Working Committee

The Health Services and International Studies Working Committee and the Late Effects and Quality of Life Working Committee conduct studies using the CIBMTR Research Database. The HSR Program complements the research of these committees, conducting studies that require additional resources and methods (e.g., surveys, focus groups, and studies involving other regional and national databases).

9.1.3 Additional Support Provided by NMDP/Be The Match Patient and Health Professional Services Department

Other functional areas of the NMDP/Be The Match augment the HSR Program in many ways, including:

- Relationships with stakeholders, including patients, caregivers, patient advocacy organizations, government agencies, and health professionals (e.g., nurses, social workers, pharmacists, physician assistants, physicians, and program administrators);
- Partnership with the NMDP/Be The Match Public and Payer Policy department, payer stakeholders, and center financial staff;

- Program planning, development, evaluation, and management for both organizational and community initiatives;
- Patient education expertise, including development of culturally and linguistically appropriate materials and resources (e.g., plain language, translations).

Health services activities that are not deemed research (e.g., patient services requests) are addressed by the NMDP/Be The Match Patient and Health Professional Services department.

9.2 KEY ACTIVITIES

9.2.1 Intramural Research Study Proposals

The HSR Program identifies and conducts research studies that fulfill the missions of and expand the research portfolios of the CIBMTR and NMDP/Be The Match. The program provides support for ongoing research activities of both organizations. It also collaborates with other CIBMTR programs, NMDP/Be The Match departments, and the BMT CTN to provide expertise for research proposals that address health policy and health services issues related to HCT and cellular therapy. External collaborators are invited to contribute expertise and resources as appropriate.

9.2.2 Extramural Research Study Proposals

The HSR Program works with external investigators interested in conducting health policy and health services research related to HCT and cellular therapy. Studies are prioritized based on relevance to the CIBMTR and NMDP/Be The Match missions, potential for extramural funding, and available resources. Specifically, the HSR Program participates in and partners on research through the ASTCT Survivorship, Palliative and Supportive Care, Biobehavioral, and Value and Health Economics Special Interest Groups.

9.2.3 Outreach

In addition to the TCT Meetings (**Chapter 16**), health services researchers participate in the following professional meetings:

- **AcademyHealth Annual Research Meeting**. *AcademyHealth* is the professional home for health services researchers and policy analysts. The annual research meeting benefits the CIBMTR and NMDP/Be The Match by providing information about the latest research methods and health policy issues as well as networking opportunities with health services researchers nationwide.
- **American Society of Hematology (ASH) Annual Meeting & Exposition**. *ASH* is the world's largest professional society for clinicians and scientists in hematology. The annual meeting provides education and highlights the latest topics in hematology.
- **International Society for Pharmacoeconomics and Outcomes Research (ISPOR)**. This international multidisciplinary professional society aims to advance the policy, science, and practice of health economics and outcomes research (clinical, economic, and patient-centered outcomes). The annual *ISPOR* conference provides information and training on the latest research methods as well as national networking opportunities.

- **Patient Centered Outcomes Research institute (PCORI) Annual Meeting**. This conference shares highlights of the *PCORI* research portfolio, including early results of completed studies and reviews of important work in progress.

CHAPTER 10: BIOINFORMATICS RESEARCH

The Bioinformatics Research team specializes in developing and utilizing software tools and analytical methods to facilitate data exchange, interpret information, understand patterns, and predict factors to save and improve lives. At the intersection of science and technology, this team pursues high impact and innovative research and produces strategic applications for the business to bridge the transition from research to operations. CIBMTR's Bioinformatics Research Program moves in the direction of computational biomedicine with activities in three main areas: Genomics / omics and high-throughput bioanalytics, machine learning and clinical predictions, and cellular therapy matching and donor registry modeling.

10.1 PROGRAM OVERSIGHT

10.1.1 Program Leadership

Bioinformatics research is led by the Senior Manager of Bioinformatics Research. Oversight for the program is provided by the Vice President of Biomedical Informatics and the Associate Scientific Director for CIBMTR Minneapolis.

10.1.2 Collaborations

The program collaborates with individuals at external organizations, such as academic centers or other registries, on a project-specific basis. Organizations with recent collaborative partnerships include:

- Bar Ilan University Department of Mathematics;
- Blood Center of Wisconsin;
- Children's Hospital Oakland Research Institute School of Medicine;
- German National Bone Marrow Donor Registry;
- German Bone Marrow Donor Center;
- Stanford University;
- Tulane University School of Medicine;
- University of California, San Francisco School of Medicine Department of Neurology;
- University of Minnesota;
    - Biomedical Informatics and Computational Biology Program;
    - Genomics Center;
    - Department of Medicine - Hematology, Oncology, Transplant;
- University of Pennsylvania, Perelman School of Medicine;
- Wesleyan University Department of Economics.

10.2 KEY ACTIVITIES

10.2.1 Genomics / Omics and High-Throughput Bioanalytics

Program staff develop processing and annotation workflows to characterize variation in donors and cellular therapy products, patients, and transplant donor-recipient pairs. The team leverages technology platforms that enable integrated, scalable data analysis and high-throughput bioanalytics on a variety of omics sources, including whole-genome, exome, protein, and methylation sequencing and microarrays. Patterns in donors and recipients are analyzed to identify associations with transplant outcomes and factors that contribute to event-free survival.

10.2.2 Machine Learning and Clinical Predictions

The Bioinformatics Research Program prepares platforms for data science applications and builds and trains models for analysis of business and clinical data collected in daily operations at the CIBMTR and NMDP/Be The Match and through network partners and research trials. Applications from search archives and donor availability, for example, provide insight into areas of future focus and improvement for NMDP/Be The Match operations. Collation and integration of 1) provider-reported clinical data and electronic medical records, 2) patient-reported data on the five areas of financial, cognitive, physical, sexual, and emotional health, and 3) in-depth collection of omics data from therapy sources and recipients, set the stage for clinical predictions and applications that the Bioinformatics Research Program investigates and develops for improving survival outcomes and quality of life for all.

10.2.3 Cellular Therapy Matching and Donor Registry Modeling

The Bioinformatics Research Program investigates algorithms to improve the prediction of missing data and the selection of cellular therapies for patients toward best survival and quality of life outcomes. Program researchers improve the collection, analysis, validation, and utilization of data on donors and patients with diverse ancestry for feature improvements. Fresh approaches leveraging graph imputation and matching are tested for accuracy, flexibility, and scalability to produce applications for NMDP/Be The Match and ensure new clinical results can be incorporated into the matching algorithm as soon as possible. Finally, the translation of research results and evidence-based guidelines to user interfaces by the Bioinformatics Research team helps to optimize cellular therapy matching and donor selection for physicians and transplant centers.

To determine how to best meet the needs of all patients in need of cellular therapy, the Bioinformatics Research Program models the composition of the Donor Registry and Biobank in order to, project and optimize the need and availability of cellular therapies for patients in need. These and related projects help to increase the likelihood of finding a match for patients who have HLA types more commonly found outside the US. The Bioinformatics Research Program also seeks to prepare a ready source of cellular therapy in case of acute radiation emergency. The Bioinformatics Research Program ensures the CIBMTR and NMDP/Be The Match are at the forefront of research and that new technologies and clinical findings can be incorporated into the operational side of the CIBMTR and NMDP/Be The Match as swiftly and seamlessly as possible.

CHAPTER 11: DATA MANAGEMENT

Data collection is a core activity of the CIBMTR that requires a comprehensive and sophisticated data management system. The CIBMTR works with federal government and international authorities to ensure essential HCT and cellular therapy data are collected, to develop data collection requirements, and to minimize the burden of data collection. These organizations (**Chapter 19**) include the:

- American Society for Transplantation and Cellular Therapy;
- European Society for Blood and Marrow Transplantation;
- Asia-Pacific Blood and Marrow Transplantation Group (APBMT);
- Foundation for the Accreditation of Cellular Therapy (FACT);
- World Marrow Donor Association (WMDA);
- Cord blood banks worldwide, and;
- Other organizations in the international HCT and cellular therapy community.

In 2006, the CIBMTR was awarded the contract for the SCTOD of the C.W. Bill Young Cell Transplantation Program (**Chapter 6**). This contract requires specialized collection and analyses of data that resulted in many changes to CIBMTR's data management practices. Of significance, the CIBMTR and the NMDP/Be The Match developed an electronic data collection system, FormsNet (**Chapter 14**), and custom forms, which are described in this chapter, for data collection including contract requirements.

Effective December 2007, the CIBMTR implemented the revised data collection forms and the FormsNet application for electronic data collection. These tools are used to collect data for the SCTOD contract requirements and all other research activities.

11.1 PROGRAM OVERSIGHT

Data management activities are shared across the two CIBMTR campuses and supervised by the Executive Director in Milwaukee and the Vice President in Minneapolis. The Customer Services Center for Data Operations provides first line assistance for CPI compliance (**Section 11.7.1**), study queries and data submission questions. New centers, centers with new data managers, and centers who have failed an audit or are on CPI consequences (i.e., probation or suspension) are assigned a Clinical Research Coordinator (CRC) for one-on-one support. The Milwaukee Program Director for Data Operations with backup from Scientific Directors serves as a medical resource for the CRC staff. Data management activities are also supported by data support staff as well as IT (**Chapter 14**) staff.

11.2 REPORTING REQUIREMENTS

Participating centers submit data to the CIBMTR at two levels:

- TED level capturing fundamental basic data;
- CRF level capturing more detail.

The TED forms contain an internationally agreed upon set of essential data elements collected for consecutive transplant recipients. TED-level data, with some additional details of donor and graft characteristics, comprise the obligatory data to be submitted to the SCTOD. CRFs capture additional patient, disease, and treatment-related data.

All CIBMTR reporting forms, including error correction and other related materials, are available on the *CIBMTR Data Collection Forms* webpage.

Generally, research studies require the more detailed CRF-level data rather than TED-level data. When appropriate, the CIBMTR shares these data with other entities.

11.2.1 TED Centers

A center designated as TED-only is required to submit the following forms:

- CIBMTR Recipient ID Assignment (CRID) (Form 2804), due only for a recipient's first CIBMTR- reported HCT or cellular therapy;
- Indication for CRID Assignment (Form 2814);
- Pre-TED form (Form 2400);
- Pre-TED Disease Classification form (Form 2402);
- Post-TED form (Form 2450) at 100 days, 6 months, annually through 6 years, then bi-annually thereafter;
- Infectious Disease Markers (Form 2004), Confirmation of HLA Typing (Form 2005), and HCT Infusion Form (Form 2006) for any recipients participating in the related specimen Repository and for all recipients of non-NMDP/Be The Match cord blood units, including autologous, related, and non-NMDP/Be The Match unrelated cord blood units;
- HCT Infusion Form (Form 2006) for all recipients of NMDP/Be The Match products [marrow, peripheral blood stem cell (PBSC), or cord blood].

11.2.2 CRF Centers

A center designated as a CRF center is required to submit the following forms:

- CRID (Form 2804), due for a recipient's first CIBMTR-reported HCT;
- Indication for CRID Assignment (Form 2814);
- Pre-TED Form (Form 2400), and Pre-TED Disease Classification form (Form 2402), followed by either the Post-TED Form (Form 2450) or a CRF (Form 2100);
- Follow-up forms, determined by the CIBMTR's forms selection algorithm (**Section 11.2.2.1**);
- Infectious Disease Markers (Form 2004), Confirmation of HLA Typing (Form 2005), and HCT Infusion Form (Form 2006) for all recipients assigned to the CRF track with one exception. Form 2004 and Form 2005 are not required for recipients of NMDP/Be The Match products as that information is reported to the NMDP/Be The Match. In addition, any recipients participating in the related specimen Repository and for all recipients of non-NMDP/Be The Match cord blood units (including autologous, related, and non-NMDP/Be The Match unrelated cord blood units) assigned to the TED-track;
- HCT Infusion Form (Form 2006) for all recipients of NMDP/Be The Match products (marrow, PBSC, or cord blood) assigned to the TED-track.

Note that the CIBMTR Research ID Assignment (Form 2804), the Pre-TED (Form 2400), and the Pre-TED Disease Classification form (Form 2402) are required on all reported patients. All personally identifiable information (PII) entered on Form 2804 is sequestered in a secured and

entirely separate database and not used for research studies. These data are accessible only to CIBMTR leadership and selected IT personnel.

11.2.2.1 Forms Selection Algorithm

The CIBMTR developed a weighted-randomization selection algorithm for CRF centers that determines which set of forms (TED versus CRF) is required for each HCT recipient. The algorithm randomly selects an epidemiologic sample of recipients for whom a CRF is to be requested. The algorithm includes, but is not limited to, type of HCT, age of the recipient, disease, etc. It gives higher weights to patients receiving HCT for rare indications, to very young and very old patients, and novel treatment approaches. It aims to provide representative, adequately sized subsets of patients for studies requiring detailed data. The algorithm is periodically reviewed to assess the burden of data submission for centers.

If any recipient consents to participate in research, the algorithm determines the HCT follow-up data submission level: Post-TED Forms or the CRFs. If an allogeneic recipient does not consent to participate in research, then the algorithm is not used, and HCT follow-up data must be submitted on the Post-TED Form.

Centers participating in BMT CTN studies (**Chapter 8**) are typically assigned CRF level status unless the trial is a post-HCT study.

11.2.3 Cellular Therapy Reporting

Cellular therapy reporting can occur pre-HCT, post-HCT, or independent of HCT.

- CRID (Form 2804), due for a recipient's first CIBMTR-reported HCT or cellular therapy;
- Indication for CRID Assignment (Form 2814);
- Pre-Cellular Therapy Essential Data (CTED) Form (Form 4000) followed by a Post-CTED Follow-up Form (Form 4100) at designated intervals, which varies by indication;
- Subsequent Neoplasms Form (Form 3500)
- Confirmation of HLA Typing (Form 2005) for all allogeneic cellular therapy donors and recipients unless already received for a prior HCT;
- Cellular Therapy Product Form (Form 4003);
- Cellular Therapy Infusion Form (Form 4006).

11.3 CIBMTR-APPROVED PROTOCOLS AND CONSENT FORMS

Research protocols exist for the Database and the Research Sample Repository (**Sections 11.3.1 and 11.3.2**, respectively). Complete participant eligibility requirements are also outlined in each study protocol.

A signed, informed consent is required of all participants on research protocols **(Chapter 12).** If the recipient of an allogeneic (related or unrelated) HCT does not consent to the use of his / her data for research, the center is still required, by US federal law, to submit TED-level data on the recipient. In this case, the recipient's data are used only for federally required analyses and reporting, such as the center-specific analysis for outcomes as mandated by CIBMTR's contract to operate the SCTOD. The recipient's data are not included in observational research studies.

TED-level data may also be used in research. Therefore, if a center only submits TED-level data to the CIBMTR, the center must still approach all HCT recipients for consent to the CIBMTR Research Database. If a recipient consents, his / her TED-level data may be used in research.

For autologous recipients who do not consent to participate in research, the CIBMTR requests only the Pre-TED (Form 2400) and Pre-TED Disease Classification (Form 2402) be submitted. This information helps ensure that the epidemiological integrity of the Research Database is maintained and does not require provision of protected health information that could identify the recipient, nor is this information used in any analysis.

11.3.1 CIBMTR Research Database Protocol

The CIBMTR Research Database is a comprehensive data source for studying HCT and cellular therapy issues including:

- Post-transplant recovery;
- Long-term outcomes after HCT and cellular therapy;
- Barriers to transplantation access;
- Donor issues, including recovery from collection procedures;
- Marrow-toxic injuries;
- Cellular therapy outcomes.

The "Protocol for a Research Database for Hematopoietic Stem Cell Transplantation, other Cellular Therapies, and Marrow Toxic Injuries" and *corresponding consent forms* are reviewed and approved by the NMDP IRB (**Chapter 12**). Centers must also submit these documents to their local IRB for review and approval or have their local IRB delegate review authority to the NMDP IRB. The CIBMTR and NMDP/Be The Match allow the consent forms to be formatted according to each site's requirements, but the protocols must be submitted as written.

11.3.2 Research Sample Repository

The Research Sample Repository stores samples for studying histocompatibility and other HCT and cellular therapy issues including:

- Tissue matching for HCT recipients and donor;
- Transplantation or cellular therapy outcomes;
- HLA tissue types in different populations (e.g., developing methods to improve tissue matching, including testing of rare HLA types).

The "Protocol for a Research Sample Repository for Allogeneic Hematopoietic Cell Transplantation, other Cellular Therapies, and Marrow Toxic Injuries" and *corresponding consent forms* are also reviewed and approved annually by the NMDP IRB. The Research Sample Repository contains blood samples from unrelated recipients and / or their adult volunteer donor or cord blood unit. Related allogeneic recipients and / or donors participate at selected centers.

11.4 IRB REQUIREMENTS

11.4.1 US Centers

All US centers must obtain IRB approval for both the "Protocol for a Research Database for Hematopoietic Stem Cell Transplantation, other Cellular Therapies, and Marrow Toxic Injuries"

and “Protocol for a Research Sample Repository for Allogeneic Hematopoietic Stem Cell Transplantation, Other Cellular Therapies, and Marrow Toxic Injuries”.

Upon obtaining IRB approval, the center must send a copy of the IRB’s approval letters, approved protocols, and informed consent documents to the CIBMTR Data Operation’s team member (**Chapter 12**). The NMDP IRB tracks the IRB approval for the CIBMTR Research Database and Research Sample Repository at each participating center. Centers that did not transition the protocols to the 2018 Common Rule requirements will receive a renewal reminder approximately two months in advance of their local continuing review date. IRB approval for these protocols must be consistent at all times with the Common Rule requirements that apply to the protocols at their center. Failure to follow the Common Rule requirements for IRB approval may affect a center’s ability to meet CPI requirements for data and sample submission.

As noted in **Chapter 12,** to be compliant with US federal regulations for human research subject protection, all centers must obtain IRB-approved informed consent from recipients to allow data submitted to the CIBMTR Research Database to be used for observational research studies, regardless of the level of data (TED or CRF) the center submits to the CIBMTR.

11.4.2 International Centers

International centers must follow their country’s laws and regulations governing human subjects and privacy protection. The center is responsible for obtaining the necessary institutional review and approval for participation in the CIBMTR Research Database. If the recipient does not consent to participate according to the respective country’s laws and regulations, the CIBMTR requests only the Pre-TED (Form 2400) and Pre-TED Disease Classification (Form 2402) be submitted. This information helps ensure that the epidemiological integrity of the Research Database is maintained and does not require provision of any protected health information that could identify the recipient, nor is this information used in any analysis. This applies to recipients of allogeneic (related and unrelated) and autologous HCT.

11.5 DATA COLLECTION FORMS

CIBMTR data collection and management activities are fully integrated across both CIBMTR campuses. A harmonized set of TED forms and CRFs is used for collecting all HCT data. A new and expanding suite of cellular therapy forms are used for collected cellular therapy data. All *data collection forms* can be viewed and downloaded at the CIBMTR website.

11.5.1 Forms Development and Revision

The CIBMTR conducts form revisions on a regular basis in response to rapidly changing technologies (e.g., molecular markers, cytogenetic prognostic factors, etc.) and internationally accepted criteria updates for disease response. The process is comprehensive involving many internal and external individuals and three levels of review. The first level involves scrutiny of data field details by subject matter experts, MS-level Statisticians, volunteer Working Committee members, Center Data Managers, and a CIBMTR Metadata Analyst who assures consistency across all forms. CIBMTR Scientific Directors, Working Committee members, and IT staff then review from a scientific and logistical standpoint. The review concludes with assessment by CIBMTR Data Operations leadership, Scientific Directors, and Senior Leadership.

Forms are released into production on a date mutually agreed upon by CIBMTR Data Operations and IT staff.

11.5.2 Forms Training

Forms training is conducted in many venues including an annual Clinical Research Professionals Data Management conference held at the TCT Meetings in February. Conference materials, including audio recordings from selected sessions are available under the *Clinical Research Professionals / Data Management Conferences* webpage.

The CIBMTR *Data Management Manual* provides detailed information about forms completion including SCTOD reporting requirements, protocols and the consent process, and instruction manuals for the Pre-TED (2400), Post-TED (2450), CRF form (2100), and some diseases including acute myelogenous leukemia, multiple myeloma, and non-Hodgkin lymphoma. CIBMTR CRCs help address issues and answer questions that may not be covered in the Data Management Manual.

The CIBMTR also provides a *Data Management Guide* that includes information about participation in CIBMTR research, center membership, data submission, data manager education, mentor program, forms submission process, and many useful tips and links.

11.5.3 Forms Submission

FormsNet allows centers to electronically submit data to the CIBMTR using both TED forms and CRFs. It includes real-time error validation, override capabilities, and access to the Forms Due Report. Periodic FormsNet updates are released to address revisions and enhancements. FormsNet also includes:

- **Verify Mobile App**. This feature enhances FormsNet security by requiring a second identity authentication. The center's primary contact is authorized to set up new users through the *CIBMTR Center Information Management* webpage. When the request is complete, the primary contact then activates the new user in FormsNet (under the maintenance tab).
- **Override Codes**. Override codes allow users to force entry of data fields that are flagged as errors in FormsNet. Errors should be assigned an override code only if the data field is confirmed as correct by center staff (e.g., Data Manager) by comparing the data field with the appropriate source document. The CIBMTR monitors each center's use of override codes.

Although centers are strongly encouraged to submit data via FormsNet, they can also submit paper forms, which can be downloaded and printed from the *CIBMTR Data Collection Forms* webpage and then faxed or mailed (postal or Fed-Ex) to the Minneapolis Coordinating Center. Upon receipt, data collection forms undergo a review for completeness and are entered into FormsNet by CIBMTR staff. Any validation errors detected by FormsNet can be corrected by the center directly through FormsNet, or Error Correction Forms can be obtained and submitted in the same manner as all other Report Forms. Electronic copies of all paper data collection forms and attached documents are imaged for future reference, and the original documents are destroyed using a secure process.

AGNIS, which was created by the CIBMTR and NMDP/Be The Match Bioinformatics, also supports secure, electronic data sharing across diverse database systems and assists centers in

collecting data for internal research, patient care requirements, and reporting purposes. For more information, view the *CIBMTR AGNIS* webpage and **Chapter 14**.

11.5.4 Forms Reimbursement

The CIBMTR reimburses centers for all completed CRFs through funds that support the Research Database. Reporting of TED-level data is not reimbursed, with the exception of Infusion (Form 2006) for NMDP/Be The Match or related recipients. When a form is designated as accurate and complete in FormsNet, the center is reimbursed according to a *fee schedule*.

The CIBMTR cannot reimburse for CRFs until it has a current, signed Data Transmission Agreement (DTA) or Master Healthcare Data and Sample Submission Agreement (MHA) on file. The DTA or MHA permits centers (both US and non-US) to transfer patient data to the CIBMTR for use in its research. This is in addition to the center's IRB approval for the CIBMTR research protocol and associated consent forms. Data Transmission Agreements are submitted to the NMDP/Be The Match Contracts department designees, who are assigned to specific centers. CIBMTR CRCs also help with forms reimbursement questions and issues.

11.6 DATA MANAGEMENT REPORTS

Data management reports support efficiency and accuracy in data collection management activities. These reports include:

- **Forms Due Report**. This report lists all Pre-TED, Post-TED, and CRFs that are due or past due for each recipient at each center. It lists the CRID Assignment of every recipient whose data were provided to the CIBMTR or NMDP/Be The Match prior to the development of FormsNet. FormsNet can generate a real-time Forms Due Report at any time and a customized report that sorts forms by specified criteria (e.g., CRID Assignment, earliest complete date, form due date, HCT date, or CPI period).
- **Forms Error Report.** This report identifies forms that have errors, listed by recipient. The report provides the form number, the question number with the error, and error description. FormsNet can generate real-time error reports at any time. Errors include missing data in mandatory fields, incorrect date or dosage ranges, inconsistency among forms (e.g., different contact dates reported on different forms), and inconsistency within a form (e.g., date of last contact occurs before initial contact).
- **CPI Reports.** This report lists the number of data collection forms that were due in a given trimester and the number and percentage of each that were completed and error-free within the specified time intervals and their CPI status. Centers receive the CPI Summary Report three times a year (January, May, and September).
- **Detailed CPI Report.** This report lists the recipients and their forms due for the trimester in which the center failed to meet CPI requirements. It also lists the forms due for the next CPI trimester. Only centers not in "good standing" on the CPI Report receive the Detailed CPI Report.
- **Daily Status Report.** This quality assurance report (for CIBMTR use only) accounts for all forms entered into FormsNet by CIBMTR data support staff each day. It helps identify error-free forms to be sent for imaging as well as forms with any errors.

- **Discrepancy Report.** This quality assurance report (for CIBMTR use only) displays discrepancies between the first and second data entry or double data entry process (**Section 11.7.3**). Designated staff members use this report to resolve any discrepancies.

11.7 QUALITY ASSURANCE PROGRAMS

11.7.1 CPI for Forms Submission

The CIBMTR monitors forms submission according to its CPI standards. To maintain CPI compliance, a center must submit at least 90% of the forms due within the time periods listed in **Table 11.1**. This includes legacy data forms that were due prior to the CIBMTR's implementation of the revised data collection process in 2007, when it launched FormsNet. The CIBMTR has developed and will implement an international CPI plan by the end of 2019. Forms must be error-free with all applicable inserts completed. Centers that are not CPI compliant enter a due process procedure.

Table 11.1: CPI Form Submission

Form	Due Date	90% Submitted Within
Pre-TED / Pre-TED Disease Classification Forms, Form 2000, Form 2814, and required disease forms and / or infection forms	HCT date	60 days
Post-TED or Form 2100 and required disease forms and / or infection forms	Day 100 after HCT	120 days
Post-TED or Form 2100 and required disease forms and / or infection forms	Six months, one year, and two years on HCT anniversary	90 days
Post-TED or Form 2100 and required disease forms and / or infection forms	Starting at year three, annually on HCT anniversary through year six, then biannually starting at year eight on HCT anniversary	45 days

11.7.2 On-Site Data Audit Program

The CIBMTR on-site data audit program includes the following steps and processes:

1) **Audit Cycle**. CIBMTR audit cycles span four years. Eligible centers, domestic and international, are assigned an audit year within that cycle. To be eligible for an on-site audit, the center must complete a minimum of 20 HCTs, including allogeneic related, unrelated, and / or autologous procedures. An audit is scheduled for the year following the performance of the center's 20th HCT. Once audited, the four-year cycle begins again for the center. The Scheduling Transplant Center Audits SOP (SOP-0149) outlines the processes for determining center eligibility for audit as well as the steps required to complete audit scheduling.
2) **Recipient Selection and Eligibility Requirements**. A pre-selected number of HCTs are audited at each center. If a center has performed more than the pre-selected number of HCTs, eligible recipient records are randomly selected (only once) for audit. A recipient record is eligible for audit only if the TED or required CRFs were submitted to the

CIBMTR and designated as complete and error-free. The Transplant Center Audit Preparation SOP (SOP-0150) details the processes for randomizing eligible recipients that will be audited, generating audit worksheets, and scheduling travel to the center.

3) **Forms and Data Fields**. All data elements on all forms are subject to audit. However, the audit concentrates on "critical" data, i.e., data most likely to be included in a research study. Data elements considered "non-critical" are randomly audited to increase the validity of the audit error rates. An average of 6,200 fields are reviewed per audit. Consent forms are also reviewed for completeness.
4) **Methodology**. Auditors compare data submitted to the CIBMTR Research Database with data from the source documentation. Discrepancies are categorized into one of three groups: Audit, missing documentation, and non-audit errors. Systemic errors may be reviewed with the Data Coordinator while the auditors are on site. Auditors make all data corrections in the Research Database, and the center is provided with a Data Change Summary report, which documents all changes; the Medical Director signs the Data Change Summary to acknowledge the changes made to the database as part of the audit. The Transplant Center Audit Process SOP (SOP-0151) outlines the processes the auditors will complete while conducting an on-site data audit.
5) **Audit Analysis and Reports**. Centers receive a detailed audit report and may be required to submit a Corrective Action Plan in response to issues identified during the audit. Issues include: 1) Critical field error rates >3%; 2) Systemic errors, e.g., consistent use of incorrect units even if the overall rate is not >3%; and / or 3) Consent form issues. The Transplant Center Audit Process SOP (SOP-0151) details the processes for entering data corrections in the Research Database, calculating audit error rates, completing and sending the audit report, and the Corrective Action Plan process.
6) **Consequences**. Any center's audit(s) resulting in a critical field error rate of >8%, two consecutive audits >5%, or three consecutive audits >3%, will result in audit consequences. Audit consequences are implemented on a case-by-case basis.

11.7.2.1 Consolidation of FACT-CIBMTR Audits

Previously, the CIBMTR and FACT individually audited data management at centers. To diminish duplications in the parallel programs and ease the reporting and compliance burdens for centers, the organizations agreed in 2016 to consolidate data management audit efforts. Within this collaboration, the CIBMTR conducts data management audits and evaluations on behalf of both organizations, and FACT determines whether the results of a data management audit are satisfactory for the purpose of accreditation.

All verification of the accuracy of data against source data is done by CIBMTR audit teams on site according to their current practices and schedules. FACT verifies at each annual report and at each application for renewal accreditation the status of CIBMTR data accuracy by requiring submission of centers' most recent CIBMTR audit results for error rates (random errors, systematic errors, and critical field error rates). FACT verifies completeness of data by requiring each center to annually submit the most recent CPI report from the CIBMTR that demonstrates "In Good Standing" related to the on-time submission of completed reports at the rate of at least 90% of expected.

Programs submitting an Annual Report or Renewal Application to FACT since January 1, 2017, undergo the new collaborative audit process. Successful FACT accreditation will depend on satisfactory completion of this process.

11.7.3 Verification and Validation

Data verification and validation are important processes to assure data accuracy and are accomplished in several ways (e.g., manually, electronically).

Double data entry of paper forms is a verification process in which two CIBMTR data support staff members manually enter the same fields from the paper form into FormsNet and their supervisor reconciles any differences between the two entries. This ensures accuracy, but also tracks the proficiency of CIBMTR data support staff. Any form fields can be manually entered into FormsNet as many times as needed for verification.

When a form is entered into FormsNet, either by the center or the CIBMTR, FormsNet performs a series of automated validation checks including:

- **Mandatory Field Validation**. This step verifies that all required fields are completed, including primary questions and their dependent fields (e.g., selecting “yes” for “developed acute graft-versus-host disease” requires answering all acute GVHD questions).
- **Range Validation**. This step verifies laboratory values, drug doses, heights, and weights against established upper and lower limits.
- **Consistency Among Forms**. This step verifies consistency between data reported on the current form and related data reported on a previous form. For example, on all forms, the contact date is validated against the HCT date.
- **Consistency Within a Form.** This step verifies each form for consistency among related data reported on the same form. For example, all dates are validated against the “date of last contact.”

If a form fails any of these online validations, an error report is generated immediately, allowing centers to correct any issues before submitting to the CIBMTR. For example, if a lab value reported on a form is outside the CIBMTR’s established validation range, the center must verify the value with the source documentation and either correct it or use an override code to remove the error. Override options include:

- NA: Not asked;
- NT: Not tested;
- UK: Unknown;
- VC: Verified correct;
- UA: Unable to answer.

11.7.4 Document Control

CIBMTR data collection forms and data management SOPs are managed through MasterControl so that controlled documents are approved, implemented, and communicated consistently. Previous versions of the documents are archived. CIBMTR forms manuals are managed through the Manula software.

11.8 ADDITIONAL DATA COLLECTION

In the event that additional data collection is approved, MS-level Statisticians coordinate special study requests with the CIBMTR CRC to request additional data from the center. These requests may also include resolving incomplete CRFs and / or missing and inconsistent data. If a study requires supplemental data collection (i.e., information not collected on CRFs), development of a supplemental form may be required prior to approaching the centers for additional data. CIBMTR staff members prepare these supplemental forms in collaboration with the relevant Working Committee after approval is obtained from the Chief Scientific Director.

11.9 CONTACT MANAGEMENT AND PERSONNEL CHANGES

The CIBMTR tracks information about centers, center personnel, Working Committee members, and other key contacts in DISCO (Data and Information for Coordinating Center Operations), which is a contact management system built on the SalesForce platform. This system has been customized to track study and publication information. Authors are linked to their contact record, which provides a more robust tracking and reporting system. A select group of staff on each CIBMTR campus has editing privileges.

The *User Access Form* allows primary contacts at centers to request new accounts and modify security access for their staff. There is also a link on the same webpage as the User Access Form that can be used to communicate center questions and changes to CIBMTR centers and their data management staff. Information is routed to a central mailbox - *cibmtr-centermaintenance@nmdp.org* - for processing.

CHAPTER 12: HUMAN RESEARCH PROTECTION PROGRAM

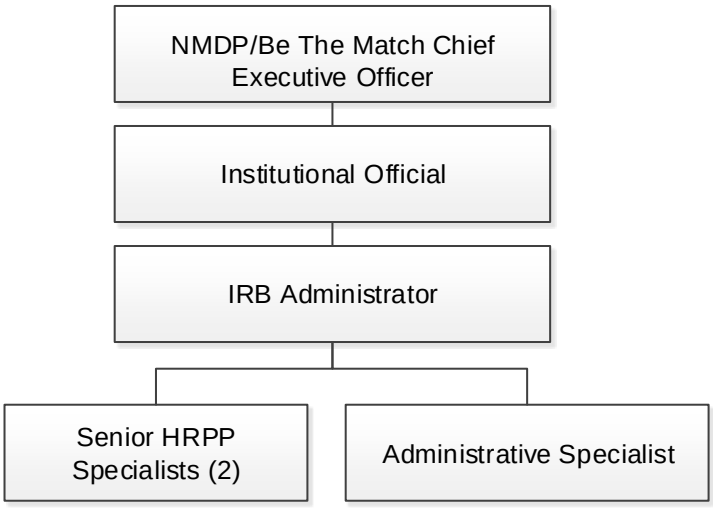
The CIBMTR works within the NMDP/Be The Match maintained comprehensive Human Research Protection Program to ensure the rights and welfare of participants in its research are protected and to ensure compliance with all pertinent US federal regulations*. In 2014, the NMDP/Be The Match Human Research Protection Program was fully accredited by the Association for the Accreditation of Human Research Protection Programs; it was re-accredited in December 2017.

Since 2011, under an IRB Authorization Agreement between MCW and NMDP/Be The Match, the NMDP IRB serves as the IRB of record for all research conducted by the CIBMTR. The NMDP IRB has the authority to approve, require modifications in, or disapprove all research activities within its jurisdiction as specified by both federal and state regulations and NMDP/Be The Match policies and procedures. The NMDP IRB reviews protocols from individual centers where the NMDP/Be The Match unrelated donor is considered a research subject by virtue of the research their recipient is participating in. The NMDP IRB also serves as the single IRB for the BMT CTN and RCI BMT. However, only CIBMTR sponsored research is addressed in this chapter. All CIBMTR staff members are required to complete initial and continuing education and training in the protection of human subjects through the *Collaborative Institutional Training Initiative*.

12.1 PROGRAM OVERSIGHT AND STAFF

Day-to-day operational activities of the NMDP IRB are overseen by an IRB Administrator, two Senior Human Research Protection Program Specialists, and an Administrative Specialist, as shown in **Figure 12.1.**

Figure 12.1: NMDP IRB Organizational Structure



* These are the Office of Human Research Protection (OHRP) common rule regulations (45 CFR Part 46) and the Federal Drug Administration (FDA) regulations (21 Code of Federal Regulations [CFR] part 50 and 21 CFR Part 56).

Members of the NMDP IRB are appointed based on their capacity to participate fully in the NMDP IRB process and are qualified through education and experience to assure a comprehensive review of the research. There are nine primary members of the NMDP IRB, including four stem cell physicians, a hematology / oncology physician, a donor advocate, a patient advocate, an epidemiologist, and an ethicist. NMDP IRB members are appointed for a three-year term, which may be renewed once.

12.2 KEY ACTIVITIES

The NMDP IRB reviews all human subject research involving CIBMTR staff. The CIBMTR research activity subject to this oversight includes all research efforts within its major Programs, which are described in detail in **Chapters 6-10**. These include:

- Observational Studies (projects implemented within the structure of its Working Committees);
- Immunobiology Research Program;
- Clinical Trials Support (i.e., RCI BMT specifically, including all Survey Research projects, and BMT CTN studies where the NMDP IRB serves as the single IRB);
- HSR Program;
- Bioinformatics Research Program.

Observational studies implemented through the Scientific Working Committee Structure that utilize data from the Research Database or specimens from the Repository are conducted under the *Research Database protocol* and / or *Research Sample Repository protocol*. All CIBMTR centers and NMDP/Be The Match donor centers are required to maintain IRB approval for the Database and Repository protocols and seek consent from patients and donors for use of their data or samples in CIBMTR research. Clinical outcomes studies approved by a Scientific Working Committee under one or both of these two protocols do not need additional IRB approval.

Studies conducted through the CIBMTR's RCI BMT or HSR Programs are also subject to oversight by the NMDP IRB. Protocols conducted through these Programs must be approved by the NMDP IRB prior to implementation. Once the NMDP IRB has approved the study, it is released to participating sites for approval by their local IRBs or for approval of their site by the NMDP IRB if the NMDP IRB is serving as their IRB of record for the study. PIs of these studies also seek IRB approval for their own site.

12.2.1 Monitoring Center IRB Compliance

As noted above, to be compliant with US federal regulations for human research subject protection, all transplant centers and donor centers participating in a CIBMTR sponsored research protocol must obtain IRB approval for the study. IRB approval letters and consent forms for all other CIBMTR sponsored research, including the Research Database and Research Sample Repository protocols, must be submitted to the CIBMTR staff designated for the specific study.

CIBMTR staff track the IRB approval at each participating center. Sites receive a renewal reminder approximately two months in advance of the center's continuing review date. The center's IRB approval for CIBMTR protocols must be current for continued participation in the protocol.

12.2.2 Investigator Support for Completing NMDP IRB Application

CIBMTR staff members involved in RCI BMT or HSR assist PIs of CIBMTR sponsored research in completing the NMDP IRB initial and continuing review applications. In addition, IRB staff members assist in the NMDP IRB application process by reviewing all submissions prior to NMDP IRB review to ensure the application is complete. Investigators with current NMDP IRB-approved studies are sent the NMDP IRB continuing review application approximately two months prior to the scheduled continuing review of the study.

CHAPTER 13: DATA - ACCESS AND RELEASE

The CIBMTR manages one of the world's largest HCT and cellular therapy outcomes research databases and is a unique information resource for clinicians, researchers, and the general public interested in HCT and other cellular therapies. It is the CIBMTR's policy to provide maximum access to and use of its data (POL-0003: CIBMTR Data Release Policy).

13.1 ACCESS TO CIBMTR DATA

Access to CIBMTR data falls into five major categories:

- Publicly available data;
- Customized requests for data and analyses;
- Requests to conduct a CIBMTR clinical outcomes study;
- Requests for datasets from previous CIBMTR research;
- Center requests for data.

The processes the CIBMTR follows for handling these requests, and timelines for completion, vary depending on the type of request, complexity, need for statistical resources, and available external funding.

The CIBMTR provides summarized, general information through its websites, described below and in **Chapter 15**. In order to efficiently handle all requests, the CIBMTR has a few common pathways to receive and triage the requests.

An MS-level Statistician is the first to receive, triage, and respond to information requests that are received via the web-based *Data Request System*. CIBMTR Scientific Directors work with the MS-level Statistician to provide scientific input, address questions, and, when appropriate, review data prior to release.

13.1.1 Publicly Available Data

The CIBMTR regularly publishes data in a variety of report formats and makes these data available through the *CIBMTR* , *NMDP/Be The Match*, and *HRSA* websites or upon request. Examples of information readily available include the annual CIBMTR Summary Slides and the SCTOD Reports (US Patient Survival Report, Transplant Data by Center Report, and US Transplant Data by Disease Report) as well as synopses of studies published by the CIBMTR. These data are provided as reports and are created to support both research and general informational uses. More information about CIBMTR websites can be found in **Chapter 15**.

13.1.2 Customized Requests for Data and Analyses

Requests that cannot be addressed using existing reports require a customized response. Reasons for these requests include self-education and decision making, patient counseling or clinical decision making, presentation support, and center assessments. They range from simple queries of patient, disease, and frequencies to those with greater complexity involving specific data combinations and / or statistical analysis of outcomes. The CIBMTR receives these requests by email or via the online *Custom Information Request Form*. Requests related to clinical decision making are responded to within three days, and results from other simple requests are generally returned within one week. Requests requiring a more complex custom analysis or dataset may take additional time, up to four weeks. If a request will take more than

the estimated one to four weeks to fulfill, the requestor will be notified of the new time estimate. Most requests will require Scientific Director review prior to sending the response. Corporate requests follow the guidelines of the Corporate Program and may require a statement of work and budget **(Chapter 17).** In other instances, the requestor may be advised to submit a formal study proposal to a CIBMTR Working Committee for approval and prioritization. Center requests may be referred to the Data Back to Centers (DBtC) web tool to obtain TED- and select CRF-level data.

13.1.3 Requests to Conduct a CIBMTR Clinical Outcomes Study

The most common request to access CIBMTR data and statistical resources is through submission of a study proposal to a CIBMTR Working Committee (**Chapter 6**). Information on how to propose a study is on the *CIBMTR How to Propose a Study* webpage. A list of previously published CIBMTR research, studies that are in progress, and copies of data collection forms are available on the *CIBMTR Data Collection Forms* webpage; investigators are encouraged to review these before submitting a proposal.

Working Committee members evaluate new proposals based on their scientific merit and feasibility as well as the CIBMTR's ability to complete the study in a timely fashion. Feedback from Working Committee members at the annual meeting is considered in deciding the relative merits of proposals. Final decisions regarding which studies to pursue are made by the Working Committee leadership and the CIBMTR Advisory Committee. Proposals may also be submitted for review by Committee leadership between meetings and may be assigned resources if deemed to be of exceptionally high impact and timeliness.

13.1.4 Requests for CIBMTR Datasets from Previous Research

The CIBMTR supports requests for datasets assembled for previously published studies and the annual Center Specific Outcome Analysis to conduct additional, independent analyses. Requestors are required to submit a study proposal using the format noted in **Section 13.1.3** to define their planned analysis and study design. These requests are for external use of the data and do not require CIBMTR statistical resources to conduct the proposed analyses. Requests for existing datasets are reviewed and approved by Coordinating Center staff. These datasets often require some review and update before they can be provided to the requestor and are accompanied by a data dictionary when distributed.

Responses to these requests are typically handled in three to four weeks but can take longer depending on complexity, verification, and approval.

13.1.5 Center Requests for Data

Many dataset requests received by the CIBMTR are from centers that submit data to the CIBMTR and are for data specific to their own center. Requestors are instructed to use the DBtC application to retrieve TED- and certain CRF-level data submitted to the CIBMTR and stored in the Research Database (**Chapter 14**). More complex requests for existing data are individually addressed by CIBMTR IT staff.

Responses to requests for existing data for centers are typically handled within two weeks but may take longer depending on the complexity of the request.

13.2 RELEASE OF CIBMTR DATA

The CIBMTR releases only datasets that comply with all relevant federal regulations regarding privacy and confidentiality. It has standard policies and procedures in place for protecting CIBMTR data; these are addressed in further detail in **Chapters 11 and 12** and the CIBMTR Data Release Policy (POL-0003).

When releasing data, the CIBMTR is obligated to ensure that datasets do not contain Protected Health Information. CIBMTR staff follow a standard procedure for creation of de-identified datasets that specifies removal of all patient, donor, and center identifiers, which could lead to the identification of a patient or center from data files. The CIBMTR does not release to the PI or any other member of his / her research team identifiable patient or center variables unless these data are critical to the approved study / project or will be used for linking to another data file via an established honest broker relationship. In these cases, special procedures are outlined in the Linking Data to External Databases or Data Sources SOP(SOP-0100) and documented with a Data Use Agreement (**Attachment to SOP-0100 and Appendix D1**) and established prior to final approval of the request.

Datasets are prepared with SAS statistical software and generally contain a standard set of essential data with pre-defined categories. A data dictionary defining each variable, valid values, and labels accompanies the dataset. Other file formats are provided upon request.

In cases of an approved traditional clinical outcomes study (**Section 13.1.3**) or when datasets are requested from previous research that will not utilize CIBMTR statistical resources for analysis (**Section 13.1.4**), the PI must submit a Data Use Agreement (DUA) that specifies the requirements for using CIBMTR data (**Appendix D1** or **D2**) before final approval of the project is offered. The DUA is provided to the PI, or requestor of data, when a study protocol or statement of work has been submitted.

13.3 PUBLISHING CIBMTR DATA

Authors requesting to reproduce CIBMTR figures or unpublished data, data in manuscripts, or other printed or online media must first receive permission from the CIBMTR and must acknowledge use of the CIBMTR's data. These requests require the use of disclaimer text and completion of the *Publication Permission Request Form* prior to publication or presentation. A letter granting the requestor permission to publish CIBMTR data includes the disclaimer text.

Responses to these requests are typically handled within one to two weeks.

CHAPTER 14: INFORMATION TECHNOLOGY SERVICES

The CIBMTR IT team is responsible for managing CIBMTR data and information, implementing commercial software products, developing custom software, and providing technical support. Responsibilities are shared between the Minneapolis and Milwaukee campuses. CIBMTR IT teams work collaboratively with each other and the NMDP/Be The Match Bioinformatics department. They support CIBMTR's scientific research objectives through the following activities, which are described in this chapter:

- Developing, maintaining, and ensuring high-quality data collection, data exchange, and data analytics systems;
- Developing and maintaining a toolkit for electronic exchange of data with centers and networks;
- Extracting SAS datasets from the CIBMTR Research Database;
- Enabling team collaboration and information dissemination by maintaining and enhancing the CIBMTR Web Presence (**Section 14.2.3**);
- Providing technical services;
- Maintaining overall security of all information systems and components in accordance with federal requirements and information security best practice.

14.1 PROGRAM OVERSIGHT AND GOVERNANCE

CIBMTR IT functionally reports to the Executive Director CIBMTR Milwaukee and the Chief Information Officer of NMDP/Be The Match in Minneapolis and is overseen by the following committees, advisory groups, and project teams.

14.1.1 CIBMTR IT Steering Committee

A CIBMTR IT Steering Committee authorizes project prioritization and scope, oversees projects, and leads key initiatives. Membership includes CIBMTR Executive Leadership and CIBMTR IT Directors. CIBMTR Program Directors and CIBMTR Functional Area Managers may be invited, as needed, based on topic areas. This committee meets monthly.

14.1.2 Advisory Groups

- **Portfolio Committees.** CIBMTR Portfolio committees provide portfolio oversight supporting operational and strategic direction. There are three Portfolio committees, with focus areas of Data Collection [(e.g., FormsNet (**Section 14.2.1.1.1**)], Data Sharing [e.g., Data Warehouse (**Section 14.2.2.3**)], and Bioinformatics (e.g. **Section 14.2.4**). These committees provide oversight, planning, and prioritization within a portfolio. They make prioritization decisions and escalate issues to the Steering Committee for review. Membership includes CIBMTR Scientific Directors, CIBMTR operational and functional leadership, and CIT Directors and program leadership. Each committee meets every other month.
- **IT Advisory Group**. This group manages project objectives, drives business process changes, and makes recommendations to the CIBMTR IT Steering Committee regarding

project prioritization. Projects occur within the following Program Areas: Data Collection [e.g., FormsNet (**Section 14.2.1.1.1**)], Data Sharing [e.g., Data Warehouse (**Section 14.2.2.3**)], Bioinformatics (e.g. **Section 14.2.4**), and Web Presence. The group also helps coordinate staff participation in IT project teams and promotes communication. It is empowered to take immediate action to resolve defects or issues that affect critical operations or data integrity. Membership includes internal leadership from functional areas who are users of CIT Systems in Data Collection, Data Warehouse, Bioinformatics, and Web Presence Program areas; subject matter experts; and CIBMTR IT Managers, Project Managers, and ScrumMasters.

- **AGNIS Sponsorship Group**. This group manages AGNIS (**Section 14.2.1.2**) project objectives and makes recommendations to the CIBMTR IT Steering Committee regarding resource allocation and prioritization. It also provides guidance in fostering relationships with AGNIS external partners. Membership includes internal leadership representing functional areas (e.g., Data Operations, IT) responsible for the AGNIS application.
- **Web Advisory Team**. This team provides ongoing management and strategic oversight of CIBMTR websites. Membership includes 10 CIBMTR leadership representatives, 3 ad-hoc member representatives from NMDP/Be The Match Marketing and Communication, and technical representation. Membership is evaluated annually. The Website Advisory Team:
    - Approves changes to messaging standards, graphic standards, the home page, programmed content and templates;
    - Conducts an annual review and audit of the websites to ensure compliance with defined standards and maintenance expectations;
    - Updates the governance and maintenance plan to support changing organizational needs or processes;
    - Identifies and proposes future development initiatives to improve site content, functionality, and site management processes.

14.1.3 Project and Scrum Teams

CIBMTR IT resources are organized based on the type of work and whether the work is part of a defined product. Project teams are responsible for the successful planning and execution of a project, which has a defined scope, beginning and an end. The CIT System Development Lifecycle SOP (SOP-0125) is followed when building software. The CIBMTR also employs Agile Scrum to iteratively or incrementally plan and deliver work that supports one or more products. Project Teams and Scrum Teams are comprised from a number of different specialties: Product owners / subject matter experts, information technology architects, project managers / scrum managers, business system analysts, programmer analysts, data analysts, quality assurance analysts, and database and system administrators.

- Activities common to both teams include:
    - Facilitating ongoing team communication;

- Collaborating on design and architecture;
- Building business readiness;
- Managing information requests.

- Project team activities include:
  - Defining business processes and requirements;
  - Completing technical design, development, and testing activities;
  - Installing and configuring software;
  - Training users on systems and processes.
- Scrum team activities include:
  - Managing scope requests, enhancements, and fixes in a product backlog;
  - Planning, designing, and executing a defined scope of work in iterative or incremental sprints.

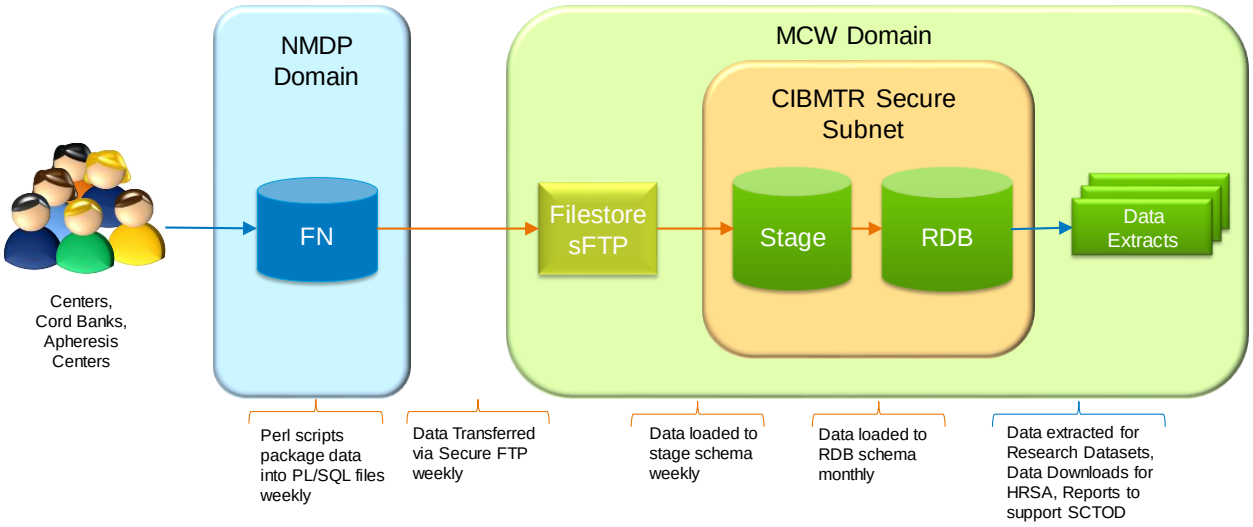
14.2 KEY ACTIVITIES

CIBMTR data systems reside within the IT structure of NMDP/Be The Match and MCW, as shown in **Figures 14.1 and 14.2**.

CIBMTR IT is responsible for managing all systems supporting the data pipeline that feeds the research activities. All data are either entered into FormsNet by Data Managers at centers or are submitted electronically to FormsNet, directly from databases or systems at the centers, via AGNIS. Although they are maintained in different registries and supported by different infrastructure, transplant and cellular therapy data follow a similar lifecycle.

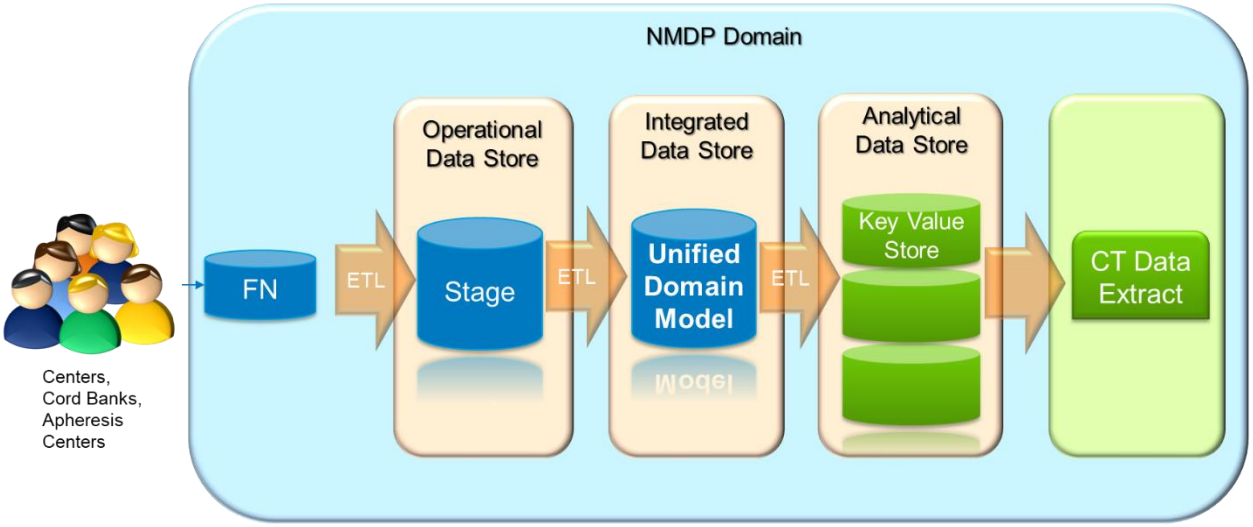
The CIBMTR Research Database contains HCT data for recipients and donors.

Figure 14.1: Research Data Flow for HCT Data



HCT data are regularly pulled from FormsNet via automated Perl scripts and are submitted via secure file transfer protocol into a staging database where an Extract, Transform, and Load (ETL) process loads the data into the Research Database. From here, a program retrieves data, summarizes it, computes common variables, and generates SAS data extracts or retrievals that are used by the Statisticians to produce study datasets for analysis. At each step in the data pipeline, additional data validations are performed to increase the quality of information available for research.

Figure 14.2: Research Data Flow for Cellular Therapy Data



Cellular therapy data are also copied from FormsNet via nightly process to staging tables within IDW. These data are extracted from IDW, using FormsNet data, and enhanced by creating calculations and aggregations from the IDW data variables. These data are used to create the Cellular Therapy Extract dataset, along with a data dictionary.

14.2.1 Data Collection Technology

14.2.1.1 Web-based Electronic Data Collection

14.2.1.1.1 Forms Net

The FormsNet application suite is CIBMTR's web-based application for data collection, submission, and forms-based storage for HCT and cellular therapy donors and recipients. It includes the following key functions:

- Electronic data submission from center to the CIBMTR for both TED forms and CRFs, including real-time error validation and forms due listings (**Chapter 11**);
- Collection of donor clearance / suitability and follow-up data to ensure donor safety;
- Support for data collection, and quality control, via the Management Reporting function;
- Support for auditing and event reporting.

14.2.1.1.2 Medidata RAVE

Medidata RAVE is the web-based electronic data capture system used for Clinical Trials and other prospective research projects. RAVE is also the system used for monitoring submitted data.

14.2.1.1.3 Electronic Patient-Reported Outcomes)

The CIBMTR's ePRO system integrates Qualtrics online surveys with PROMIS computer adapted test measures and a Salesforce Customer Relationship Management platform to administer quality of life and other patient-reported outcomes with follow-up support by the Survey Research Group.

14.2.1.2 AGNIS

AGNIS is a messaging middleware that permits electronic submission and retrieval of forms data with FormsNet. The CIBMTR and NMDP/Be The Match Bioinformatics created this messaging conduit to assist centers in collecting data for internal research, for tracking patient data to assist in care management, and for reporting purposes. AGNIS supports secure data sharing across diverse database systems. The AGNIS software is an open-source web service distributed under a public license at *AGNIS.net* and is available to any interested center.

Data are transmitted via AGNIS using common data elements (CDEs) from the Cancer Data Standards Registry and Repository (caDSR), a metadata repository operated by the NCI Center for Biomedical Informatics and Information Technology. It is compliant with government standards for electronic data transmission. Nearly all data fields collected in FormsNet are represented as CDEs within caDSR.

14.2.2 Data Sharing

The CIBMTR Data Release Policy (POL-0003) is reviewed and approved annually by senior leadership.

14.2.2.1 Research Database

The CIBMTR Research Database contains all HCT and cellular therapy data collected by the CIBMTR as well as historical data collected on IBMTR and NMDP/Be The Match forms. These data are represented in a centralized, domain-based relational model, rather than the forms-

based model used in FormsNet, to better support data integration across forms. The CIBMTR-developed ETL program extracts form-based, vertical FormsNet data and then transforms and loads the data into the domain-based model in the CIBMTR Research Database. This program also performs cross form and longitudinal data integrity checks.

14.2.2.2 SAS Retrieval

CIBMTR Biostatisticians perform analyses using third-party *SAS software* applications for clinical data analyses and reporting. To simplify study dataset preparation, CIBMTR IT staff creates SAS datasets of the most commonly analyzed data fields and most commonly used computed variables. The data are extracted from the CIBMTR Research Database and formatted to be SAS-compatible. Eight datasets are created with different levels of frequency throughout the year, as shown in **Table 14.1**. The Data Retrieval SOP (SOP-0048) details the specific steps in this process.

Table 14.1: Study Datasets

Study Datasets	Description
TED	All transplants (legacy NMDP, IBMTR, and FormsNet). Includes data on Pre-TED (Form 2400), Pre-TED Disease (Form 2402), Post-TED (Form 2450), including equivalent data derived from CRF track, cord blood data (Forms 2004, 2005, 2006) forms.
Cellular Therapy Extract*	All cellular therapy infusions where at least a F4000 has been reported. Includes data on Pre-CTED (Form 4000), Disease forms (Form 2402, Plasma Cell Disorders (PCD) Pre / Post HCT Forms 2016/2116, LYM Pre / Post HCT Forms 2018 / 2118), Post-CTED (Form 4100), including equivalent data derived from HCT tracks, HLA (Forms 2005) forms. *This extract is not in a SAS retrieval format.
HCT Allogeneic	All transplants for patients on CRF track who had an allogeneic transplant and a follow-up form was submitted. Includes data from CRF forms (Forms 2000, 2100, 2900, 2004, 2005) and disease forms.
HCT Autologous	All transplants for patients on CRF track who had an autologous transplant and a follow-up form was submitted. Includes data from CRF forms (Forms 2000, 2100, 2900, 2004, 2005) and disease forms.
Study	All patients in certain studies for which immediate access to all data submitted is critical; examples include corporate studies and BMT CTN trials. Includes data from CRF forms (Forms 2000, 2100, 2900, 2004, 2005) and disease forms.
TED Retrieval to support SCTOD	Allogeneic transplants performed after 12/03/2007. Includes only Pre-TED, Pre-TED Disease, Post-TED (including equivalents from CRF track), and cord blood data. Submitted quarterly to the HRSA.
DBtC	All transplants for centers including legacy IBMTR since 1972 and legacy NMDP to 1987. Includes only Pre-TED, Post-TED (including equivalents from CRF track). Retrieval is completed quarterly and posted on the CIBMTR Portal for access by authorized users of centers.

Study Datasets	Description
eDBtC	All transplants for centers since 1/1/2008. Includes most commonly used select data from Pre-TED and Post-TED forms, as well as data from CRF Forms (2000, 2100, 2900, 2004, 2005, disease). Data are extracted monthly and populate the eDBtC data model in the Qlikview data analytics application, which is hosted on the CIBMTR Portal for access by authorized center users.

14.2.2.3 Data Warehouse

Work continues on the IDW to consolidate CIBMTR systems and support the utilization of quality data that meet the diverse administrative and scientific needs of CIBMTR stakeholders. The CIBMTR has pursued an evolutionary approach to implementing the IDW in a way that does not compromise our ability to fulfill existing obligations. When complete, the IDW will provide data sharing products that fulfill desired capabilities, including:

- Access to and export of data for research analysis;
- Performance management;
- Quality data monitoring;
- Compliance with requests from regulatory bodies, accrediting organizations and payers.

The IDW will support these capabilities through different information delivery methods including reports and dashboards, applications, data extracts, and self-service analytics.

14.2.3 Web Presence

The primary goals of the CIBMTR Web Presence are to optimize and enhance CIBMTR websites to:

- Provide better online access to HCT and cellular therapy information for both the scientific community and the public;
- Provide training and support to centers who provide outcomes data to the CIBMTR;
- Create a shared communications and networking environment for centers and CIBMTR Working Committees;
- Provide web-based access to CIBMTR databases and other resources.

CIBMTR's Web Presence initiative comprises three distinct websites, each with its own purpose and security model:

- **Public website**. The public website *CIBMTR.org* is unrestricted and provides information about the CIBMTR, its data collection process, research activities, committee structure, how to get involved, news, and publications. The CIBMTR Summary Slides (**Chapter 13**) are posted annually on the site in a downloadable PowerPoint format. These frequently requested slides summarize outcomes and current uses of HCT and provide answers to questions posed by the research community. The public website also provides information from CIBMTR's Studies, Publication, and Authors Database, which includes more detailed information about studies, publications (since 1972), and historical information on authors and their institutions.

- **Collaborate website**. *Collaborate* functions as CIBMTR's intranet and primary collaboration portal. Deployed in SharePoint, Collaborate provides features that promote cooperation among CIBMTR staff and serves as a communication platform for specific studies and initiatives. This secure site requires a username and password. Access is based on a user's assigned role.
- **Portal website**. The *Portal* website functions as a secure extranet that delivers custom applications and data to CIBMTR staff and partners (including investigators), centers, and CRCs. It provides access to the following applications:
    - **Data Back to Center (DBtC)**. The DBtC application permits US centers (generally the Medical Director or primary data contact only) to download data (in either XML or comma-separated value format) that have been validated and processed into the CIBMTR Research Database. DBtC provides access to a center's data that have been validated by the rules in the ETL system and transferred to the Research Database; it also includes the total number of forms submitted. These data are updated quarterly, and the DBtC Quarterly SAS Data Load Process SOP (SOP-0050) details the specific steps in this process. A data dictionary is provided with definitions for each field and coded values in the datasets.
    - **Enhanced Data Back to Center (eDBtC)**. eDBtC is a data analytics product that provides users with self-service access to a subset of their most commonly used data, including functionality to analyze and view descriptive statistics and outcomes. Predefined filters permit analysis of subsets of interest and robust visualization features provide options for viewing data in a chart or table. eDBtC also enables users to view and filter outcomes, including 5-year overall survival, acute and chronic GVHD, and other outcomes for populations of interest. An ad-hoc query tab permits users to create and implement custom queries. eDBtC data are extracted, validated, and refreshed monthly. Users can export data in Excel file formats. The eDBtC Monthly Load Process SOP (SOP-1151) details the specific steps in this process. All data that supports the tables and charts can be easily downloaded. Plans are underway to extend eDBtC with additional HCT and cellular therapy variables and to provide functionality to users interested in aggregating data from multiple centers (with agreements), such as cord blood banks or to support clinical trial feasibility and eligibility assessment.
    - **Patient One-Year Survival Calculator**. The Patient One-Year Survival Calculator for Allogeneic Transplants is deployed on the portal for access by Medical Directors. The intent of this online survival calculator is to provide centers with a tool to predict one-year survival for individual allogeneic HCT recipients. Data taken from the CIBMTR Center Specific Survival Report for 2019 is used to calculate the expected probability of one-year survival for individual recipients of

first allogeneic HCT in the US. Patient, disease, and transplant characteristics of allogeneic HCT recipients at US centers between 2015 and 2017 are currently used to generate these estimates. The Survival Calculator Information and Update Process SOP (SOP-0055) details the specific steps in this process. The calculator is updated annually to reflect new information contained in the center outcomes analysis.

- **Center Volume Data Report (CVDR)**. The CVDR allows centers to review and approve center volume data that is published annually to the *Bone Marrow and Cord Blood Donation and Transplantation* website to which the CIBMTR is required to provide data. This public website, under the Department of Health and Human Services banner, is required by the SCTOD contract (**Chapter 6**) and includes the center-specific outcomes data collected by the SCTOD. The CVDR displays and permits download of the previous two years of volume data in addition to the current year. Subsequent reports show additional HCTs performed since the data were last approved.
- **Center Performance Analytics (CPA)**. CPA supports center performance and quality initiatives using the dataset from the Transplant Center Specific Survival Analysis. Authorized (by center) users can compare their center's data relative to aggregated data from other centers using predefined filters that include geographic region, historical performance, volume of HCTs, and patient population served. Centers can visualize and filter their center's own one-year survival rate, based on the rolling three-year period of data included in the Analysis dataset. Like eDBtC, users can create and implement customized, ad hoc queries and export a download of the source dataset for their center. CPA is updated annually, and the Refresh Data for Center Performance Analytics SOP (SOP-0117) details the specific steps in this process.
- **Data for Request for Information (RFI)**. Data for RFI is a QlikView / Microsoft Excel solution that utilizes the standard reporting format developed by the ASTCT and provides US centers with the ability to access, view, reconcile, and format data previously submitted to the CIBMTR to fulfill the center's annual obligation to share outcomes data with third party payers and external organizations. Accessible from within the eDBtC application, Data for RFI leverages the same CIBMTR data available in eDBtC but translates it to the standard RFI format developed by the ASTCT, including but not limited to risk classification by disease. It also incorporates the standard ASTCT rules for determining survival, differentiating between adult and pediatric populations, and more. Data for RFI is not a report but a data extract that centers can export in an Excel document that conforms to the standard format developed by the

ASTCT. It does not contain data not collected on CIBMTR forms or not provided to the CIBMTR.

- **PartnerShare.** PartnerShare provides research collaborators and study sponsors that have obtained required approvals and executed contracts with CIBMTR with self-service access to data on patients submitted across centers based on specific protocol criteria, such as therapeutic product used, disease indication, or cohort characteristics. Data will be refreshed monthly. Users can export data in Excel file formats. Initial data visualization features will provide accrual information by study and center query status. Predefined filters permit analysis of subsets of interest and robust visualization features provide options for viewing data in a chart or table.

14.2.4 Bioinformatics Supported by IT Services

Bioinformatics Research is described in **Chapter 10**. CIBMTR IT services provides data, infrastructure, security, and systems administration support for Bioinformatics Research in the areas of registry and donor selection optimization, matching algorithm improvements, and other data acquisition and analysis capabilities.

- **Registry and Donor Selection Optimization**. Donor registry diversity analysis is provided by CIT in addition to support for bioinformatics services on HLA typing resolution score, donor readiness score, HLA genotype frequency score, and additional related tools for registry analysis and optimization of availability and selection of donors.
- **Matching Algorithm Improvements**. CIT provides support for Bioinformatics research on graph imputation and matching outcome and feature improvements, including scalability and flexibility. Processing and updates for research matchgrades required and requested by Working Committees and other stakeholders are also provided.
- **Data Acquisition and Analysis Capabilities**. Other data acquisition and analysis capabilities are supported by CIT, including the management and preservation of search archives and preparation of datasets for machine learning and analytics. Infrastructure support for cloud computing, omics workflows, and data science platforms is provided by CIT in addition to support for other data science enablement.

14.2.5 Technical Services

CIT departments on both campuses work collaboratively with the parent IT departments at MCW and NMDP/Be The Match to provide technical service support for servers, networking equipment, and personal computers. This includes shared file directories, email systems, operating systems, software patches, service monitoring, firewalls, and user accounts and permissions. Staff service requests are submitted to the respective IT departments.

14.2.6 Information Security

The CIBMTR maintains comprehensive information security and data protection practices that align with the National Institute of Technology and Standards (NIST 800-53) Security and Privacy Control for Federal Systems framework as well as the policies and procedures of the CIBMTR and its parent institutions, the MCW and the NMDP. These practices are continuously monitored and subject to annual assessment by a qualified, independent third-party auditor. Assessment findings and a statement of fact are reported to the CIBMTR Information Security and Data Protection Committee for acceptance and, upon request, are made available as part of a security assurance package to key stakeholders, including HRSA.

CIT systems security oversight include:

- **Ongoing Maintenance of Hardware and Software Inventories**. The Maintaining CIT Information System Component Inventory (SOP-0160) details the specific steps in this process.
- **Ongoing Management of User Accounts and Privileges**. The FormsNet3 Account Management SOP (SOP-0163) details the specific steps in this process.
- **Incident Reporting**. As detailed in its SOP (Plan-0002: CIBMTR Incident Response Plan), the CIBMTR will fulfill the Incident Response requirements as described in the SCTOD contract, as appropriate, report to the HRSA Office of Information Technology.
- **Monthly Vulnerability Scans and Regular Patching**. The Vulnerability Scanning and Remediation SOP (SOP-0059) details the specific steps in this process.
- **Ongoing Configuration Management Review Board Meetings**. The Configuration Management for Systems / Data SOP (POL-0009) details the specific steps in this process.
- **Annual Contingency Plan Testing**. The Contingency Planning Policy (POL-0018) details the specific steps in this process.
- **Annual Incident Response Testing**. The Incident Response for Data / Systems Policy (POL-0019) details the specific steps in this process.
- **Annual Review and Update of Information System Security Plan Documents**.
- **Annual Security Awareness Training**. The Security Awareness and Training Policy (POL-0005) details the specific steps in this process.

The CIT security plans substantially enhance information system security risk management and are more robust than the standards established by Health Insurance Portability and Accountability Act of 1996 (HIPAA), which provides federal protections for personal health information (**Chapter 12**).

14.2.7 Data Use and Protection

The CIBMTR conducts security control assessment annually, most recently in July 2018 by a qualified, independent third-party auditor, Baker Tilly Virchow Krause, LLP. The CIBMTR continues to work with HRSA to determine the applicability of and renewal timeline for the 2015 Authority to Operate designation. The NMDP/Be The Match also holds an Authority to

Operate from HRSA, ensuring similar standards of information security are applied to all CIBMTR and NMDP/Be The Match systems, including the FormsNet data collection system. These controls maintained by the CIBMTR and NMDP/Be The Match represent robust information security risk management beyond those outlined by HIPAA.

In response to changing global personal data protection requirements, the CIBMTR reviewed and updated its Data Use and Processing Policy (PDF) in 2018. A Personal Data Protection Statement is publicly posted on the CIBMTR website along with additional information regarding CIBMTR security infrastructure and how it protects personal data. The CIBMTR understands the importance of its role as a steward of the data it collects and continues to work with domestic and international partners to ensure its systems meet all standards.

CHAPTER 15: COMMUNICATION

This chapter defines how the CIBMTR communicates internally and its outreach to key external partners, including center staff, physicians, working group members, and the general public. The communication strategies for these activities are to:

- Build a consistent image and understanding of the CIBMTR and related organizations;
- Develop simplified, succinct, and clear communications about research, research services, data, and expertise;
- Develop benefit- and action-focused communications to motivate stakeholders.

15.1 OBJECTIVES AND STRATEGIES

To promote its research efforts and meet the needs of its various audiences, the CIBMTR defines and prioritizes communication objectives to raise awareness about the CIBMTR, develop meaningful content, implement key activities, and increase stakeholder and resource support. These objectives seek to:

- Increase understanding of the CIBMTR and its contributions (e.g., supporting high-quality studies including proposals, trial enrollment, and timely completion of research);
- Increase participation in and commitment to CIBMTR research (e.g., encouraging current and new leaders to submit studies and collaborate on research projects);
- Improve efficiency and engagement in data submission (e.g., ensuring that data managers are well-trained and efficient);
- Increase use of CIBMTR data and expertise to advance transplantation and cellular therapy (e.g., promoting use of the Research Sample Repository).

To accomplish these objectives, communication strategies are to:

- Raise awareness of the CIBMTR, CIBMTR studies, and study impact leading to practice-changing findings;
- Raise awareness of availability of and methods for accessing CIBMTR research services, data, and expertise;
- Engage young physicians in the CIBMTR by offering CIBMTR services to help them perform research and meet publishing goals;
- Simplify and improve training, communications, and support for data submission;
- Generate interest in increasing level of participation in CIBMTR research / Working Committees by emphasizing benefits to clinician (individual and institutional);
- Engage corporations and organizations in supporting CIBMTR research and meetings.

15.2 STANDARDS

The CIBMTR uses a standardized brand, or appearance, that represents the organization and makes it recognizable to its various audiences. An ongoing committee with bi-campus representation helps develop and maintain these brand standards and makes recommendations for graphics (including logos), numerical displays, documentation, and language. The Website Advisory Team, which oversees the public and two private websites (**Chapter 14**), maintains consistent appearance and processes. The *CIBMTR Brand Standards* document is available for download in Collaborate.

15.2.1 Acknowledging the CIBMTR in Publications

The CIBMTR encourages use of the following standard texts, as applicable, whenever the CIBMTR is described in print materials:

- **General Acknowledgement**. The CIBMTR collaborates with the global scientific community to advance hematopoietic cell transplantation and cellular therapy research worldwide. A research collaboration between the National Marrow Donor Program®/Be The Match® and the Medical College of Wisconsin, the CIBMTR facilitates critical, cutting-edge research that has led to increased survival and an enriched quality of life for thousands of patients. Its prospective and observational research is accomplished through scientific and statistical expertise, a large network of centers, and a clinical outcomes Research Database of more than 500,000 patients.
    - **Negative Acknowledgement** (used when the CIBMTR does not agree with published findings or interpretations). The CIBMTR did not review and / or approve the study results presented in this publication.
- **Data Sources Statement** (**Appendix F**).

Use of the appropriate acknowledgement in the publication is approved by the Senior Scientific Director for Research Operations.

15.3 KEY PERSONNEL

Key personnel within the Business Development functional area, and on both campuses, provide input to and approval for a variety of CIBMTR materials prior to publication. Additionally, the NMDP/Be The Match Communication and Marketing staff contributes to the development and support of objectives and strategies, including content development of internal and external communication tools for certain CIBMTR outreach activities.

15.4 KEY ACTIVITIES

Development and dissemination of information is a core activity of the CIBMTR. Information must move effectively and efficiently from the Coordinating Center as well as between and within Working, Steering, and Advisory Committee members; investigators; center staff; and others to promote high-quality HCT and cellular therapy research.

The CIBMTR is committed to collaborative work with all its partners and works to overcome communication barriers, including geographical and time zone differences, language, security concerns, and research goals. To ensure productive communication among collaborators, the CIBMTR encourages face-to-face meetings when feasible as well as teleconferences, and it supports several communication mechanisms.

15.4.1 SharePoint Collaborate

The CIBMTR uses Collaborate, a password-protected collection of SharePoint websites for secure document sharing, internal communication between campuses, and use by employees working off-campus. Collaborate is also used for departmental, functional, process-related, and collaborative project activities.

Collaborate continues to be enhanced and organized on an ongoing basis to optimize and strengthen internal and external communication. Examples of these activities include collaboration to enhance products, including FormsNet, AGNIS and other application

developments and collaboration on projects like the Integrated Data Warehouse. Collaborate also supports collaboration on data governance, data quality management, SOP process and document management, TCT Meetings and other meeting administration, Working Committee collaboration, and knowledge management. Workflow processes and Working Committee study collaboration features are also being expanded (**Chapters 6, 11, 14** and **16**). Collaborate is only available to registered users, and users are assigned privileges for specific site and / or file access depending on their role and credentials.

15.4.2 Conference Attendance

National conferences are key opportunities to interact in person with many audiences. They not only provide a wide range of educational opportunities for CIBMTR staff members, they also help educate others about the range of research and educational activities of the organization. The CIBMTR hosts exhibit booths at selected conferences, which provide opportunities to:

- Share CIBMTR publications;
- Share informational marketing materials;
- Network with colleagues and interested investigators.

15.4.3 Websites

The CIBMTR "Web Presence" initiative includes three distinct websites, each with its own purpose and security model:

- The Public website *CIBMTR.org* is unrestricted and provides information about the CIBMTR and its research;
- The *Collaborate* website promotes connectivity among CIBMTR staff members and a communication platform for specific studies and initiatives;
- The *Portal* website delivers custom applications and data to CIBMTR staff and partners, including Investigators, centers, Clinical Research Coordinators, and commercial partners.

Requested updates to any of the CIBMTR websites should be submitted via the *Web Change Request Form*.The Website Advisory Team (WAT) processes each request and seeks necessary approval for each change. Additional questions regarding a website change should be sent to *cibmtr-webmaster@mcw.edu*.

For more information about these websites, see **Chapter 14**.

15.4.4 Summary Slides

Each year, the CIBMTR publishes Summary Slides on the state-of-the-art in BMT. Using information from the CIBMTR Research Database, an MS-level Statistician and a CIBMTR Senior Scientific Director prepare these charts summarizing current uses and outcomes of allogeneic and autologous HCT. These valuable and highly anticipated slides are used by clinicians and researchers in the transplant community. *Summary Slides* are posted on the CIBMTR Slides and Reports webpage (under Reference Center).

15.4.5 Publications

The CIBMTR produces increasing numbers of peer-reviewed publications as well as book chapters. Most are submitted from the Coordinating Center. All NIH requirements, including PubMed citations, and specific journal guidelines are followed, including proper acknowledgment of funding resources. See **Chapter 3** for authorship rules. A *current list of publications with citations* is maintained on the CIBMTR Publication list webpage (under Reference Center).

15.4.6 Lay Summaries

The CIBMTR creates easy-to-read summaries of publications (CIBMTR and BMT CTN) for the lay public. Summaries are created through a collaborative process involving CIBMTR Consumer Advocacy Committee members, a CIBMTR Medical Writer, a CIBMTR Communications Specialist, an NMDP/Be The Match Patient Education Specialist, and CIBMTR Scientific Directors / BMT CTN Protocol Chairs. Additional information can be found in the CIBMTR Research Publication Summaries for Patients SOP (SOP-0024). Once finalized, the summaries are posted on the *CIBMTR Study Summaries for Patients* webpage. The Patient-Friendly Summaries of CIBMTR Research Publications SOP details the specific steps in this process.

15.4.7 Post-Transplant Guidelines

The CIBMTR, along with several other organizations, publishes recommended post-transplantation treatment strategies. NMDP/Be The Match converted these strategies into an easy-to-use reference guide for physicians and patients. It is available in print, online, and in a mobile application (for iPhone® and Android™). The guidelines can be accessed on the *CIBMTR Post-Transplant Guidelines* webpage, and they are published [Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation; CIBMTR, American Society for Blood and Marrow Transplantation, European Group for Blood and Marrow Transplantation, Asia-Pacific Blood and Marrow Transplantation Group, Bone Marrow Transplant Society of Australia and New Zealand, East Mediterranean Blood and Marrow Transplantation Group and Sociedade Brasileira de Transplante de Medula Ossea. Co-published in Biology of Blood and Marrow Transplantation, 2012; 18(3): 348-371; Bone Marrow Transplantation, 2012; 47(3): 337–341; and Hematology/Oncology and Stem Cell Therapy, 2012; 5(1): 1-30].

15.4.8 Annual Reports

The CIBMTR publishes two annual reports. Both fulfill requirements of cooperative agreements with NCI, NHLBI, and NIAID, as the major source of funding for the fundamental work of the CIBMTR, and with the NHLBI and NCI for the DCC of the BMT CTN (**Chapter 8**).

Two versions are prepared for each of the annual reports. One is submitted to the government to fulfill grant requirements, and a second version is prepared for website posting and distribution at public meetings. The primary audience for the public versions is the scientific community, researchers, and the general public. Printed copies are created for distribution of the public versions. Electronic copies are available on the *CIBMTR Administrative and Progress Reports* webpage and the BMT CTN *Progress Reports* webpage.

The CIBMTR government annual report details accomplishments and goals of the previous calendar year. The public version is published and distributed during the TCT Meetings in

February. A prominent feature of the public version is the easy-to-read format with many colored figures and call out boxes. The CIBMTR Annual Progress Report SOP (SOP-0037) details the process for creating and distributing both the public and government versions of the report each year.

The BMT CTN Progress Report details accomplishments and goals of the DCC during the previous 12-month reporting period. The public version is distributed for the first time during the annual summer meeting of the BMT CTN Steering Committee. The prominent feature of it is the detailed review of each clinical trial: Completed trials, those actively accruing patients, and those under development or consideration.

15.4.9 Newsletters

The CIBMTR publishes a quarterly newsletter for the HCT and cellular therapy community. The newsletter is distributed via email and posted on the *CIBMTR Newsletters* webpage. The primary audience is center physicians and staff who participate in CIBMTR research by submitting data. Newsletters feature updates on CIBMTR Working Committees, research programs, data collection and management, and newsworthy events in the HCT and cellular therapy community.

15.4.10 Social Media

The CIBMTR maintains Twitter (*@CIBMTR*) and Facebook (*@theCIBMTR*) accounts to increase awareness of the organization, collaborate with various individuals both within and outside the HCT and cellular therapy research community, and share resources. The CIBMTR Communications Specialist monitors, updates, and posts content to these accounts on a regular basis, providing information and supporting the CIBMTR's network.

15.4.11 Informational Marketing Materials

Any program, department, or committee can have need for materials to inform or explain. The communications staff at either campus may produce these materials with input from appropriate personnel on either campus. These materials may include flyers for distribution at meetings, the CIBMTR overview brochure, documents for Working Committee members and centers, and others.

For example, during the TCT Meetings, the BMT CTN distributes not only its annual report (described above) but also an annual Summary of Accomplishments as well as protocol flyers, which list the treatment schemas of ongoing protocols and those near activation.

15.4.12 Phone, Video, and Web Conferences

Conference calls, video conferencing, and web conferences are utilized by many CIBMTR functional areas to optimize communication and productivity between groups that may be spread apart geographically. Teleconferencing helps create interpersonal relations and increased collaboration among the CIBMTR, its associate institutions, and its research partners. For example:

- CIBMTR Working Committees utilize conference calls among Scientific Directors, PIs, and various committee members to discuss current studies and proposals for future studies.

- The CIBMTR IT group, which has members on both campuses, utilizes conference calls and video conferencing to facilitate collaboration between the Milwaukee and Minneapolis campuses as well as with NMDP/Be The Match Operations staff.
- The CIBMTR Coordinating Center also has members on both campuses as well as in the Department of Biostatistics at MCW and brings these members together for weekly teleconferences to discuss ongoing statistical development of research protocols.
- Clinical Research Coordinators, Data Support staff, Program Coordinators, and Administrative staff utilize conference calls to complete a wide range of responsibilities.
- The following groups also use conference calls and video conferencing as a primary interface: Executive Committee, Consumer Advocacy Committee, Affiliation Board, Protocol Writing Committees, and many more.

15.4.13 Dissemination through NMDP/Be The Match

CIBMTR research results and outcomes data are also routinely highlighted through the medical education activities of NMDP/Be The Match, reaching US and international audiences online at BeTheMatchClinical.org, through newsletters, during medical education programs, via clinical resources, and more.

15.5 EDUCATIONAL OUTREACH

15.5.1 Data Management Education

The CIBMTR has provided data quality training to contributors for more than 20 years. The CIBMTR continues to offer in-person training sessions in conjunction with the TCT Meetings, as these sessions offer an invaluable opportunity for the CIBMTR and center staff to interact personally and share best practices. In-person training includes topics such as pertinent diseases, complications post-HCT like acute or chronic GVHD and infections, long-term outcomes, etc.

The Data Operations Trainer along with the Learning Development Specialist create web-based training modules to assist data contributors around the world. The currently available training modules address core competencies such as the general process, basic review of applicable science including pertinent diseases, medical terminology, immunology, hematology, histocompatibility, reporting documents and schedules, and CIBMTR policies and procedures.

Ongoing, comprehensive web-based training helps address the problems caused by turn-over in data management staff at centers, the wide geographic distribution of centers, and limited resources overall for supporting attendance of all data management staff at in-person meetings. Detailed documentation also helps train center staff to report in an accurate and timely manner. The CIBMTR has produced a detailed instruction manual for the CRFs as well as the Pre- and Post-TED forms. There are disease-specific instruction manuals on the *CIBMTR Forms Instructions Manual* webpage including:

- Acute myelogenous leukemia (AML);
- Acute lymphocytic leukemia (ALL);
- Chronic myelogenous leukemia (CML);
- Chronic lymphocytic leukemia (CLL);
- Myelodysplastic syndrome / myeloproliferative neoplasms (MDS/MPN);

- Juvenile myelomonocytic leukemia (JMML);
- Plasma cell disorders (PCD);
- Hodgkin / non-Hodgkin lymphoma (HL/NHL);
- Waldenstrom's macroglobulinemia (WM);
- Aplastic anemia;
- Immune deficiencies (ID);
- Wiskott-Aldrich Syndrome (WAS);
- X-linked lymphoproliferative syndrome (XLP);
- Hemophagocytic lymphohistiocytosis (HLH).

Additional disease-specific instruction manuals are posted as they are completed.

15.5.2 BMT CTN Coordinator Education

The first BMT CTN (**Section 8.1**) Coordinators Meeting was held in conjunction with the BMT Tandem Meetings in February 2008. The goal was to present a variety of logistical and scientific information geared towards Center Research Coordinators. This popular meeting is now scheduled annually during the TCT Meetings.

The BMT CTN Coordinators meet typically for a day, during which they cover a variety of topics ranging from data entry and quality control issues to review of procedures and protocol requirements. The Coordinators provide the DCC with useful feedback from centers. The BMT CTN also hosts a BMT CTN Investigators Meeting, which BMT CTN Coordinators are invited to attend. The BMT CTN Investigators Meeting features BMT CTN Protocol Chairs sharing results from completed studies or presenting upcoming studies.

15.5.3 RCI BMT Training

RCI BMT (**Section 8.2**) staff members provide protocol-specific training to sites participating in a protocol. Prior to the activation of a clinical trial at a selected site, a Site Initiation training will take place with the study site to train the PI, coordinator and supporting study staff on the objectives and procedures of the study. This will take place remotely via conference call, web-based conferencing, eLearning training sessions or during an onsite face-to-face training. If applicable, the meeting can take place in person either at the site or another location. Training content includes study overview and purpose, summary of Good Clinical Practices, summary of the study design and study procedures, review of Inclusion and Exclusion criteria, subject enrollment procedures, assessments, follow-ups, adverse event and unanticipated problem reporting, case report form review, and electronic data capture system training along with any other study specific procedures (e.g. labs, drug accountability). If staff changes occur during the protocol, training will be provided.

CHAPTER 16: MEETINGS

The annual Transplantation & Cellular Therapy Meetings of the ASTCT and the CIBMTR (TCT Meetings), formerly known as the BMT Tandem Meetings, have been co-hosted by the CIBMTR, and its predecessor, in collaboration with the ASTCT since 1993. These meetings are a well-recognized forum for HCT and cellular therapy physicians, scientists, allied health professionals, and others. Discussions focus on idea generation, works in progress, and reporting of completed projects. CIBMTR personnel also participate in other scientific meetings as attendees, presenters, and booth hosts. The most prominent of these are the NMDP/Be The Match Council Meeting held in November, the ASH Annual Meeting held in December, the EBMT Annual Meeting held in spring, and the ASCO Annual Meeting in June.

16.1 TCT MEETINGS

The TCT Meetings are the combined annual meetings of the CIBMTR and the ASTCT. They are the largest gathering in North America of worldwide experts in HCT and cellular therapy patient care, clinical investigation, and laboratory research. Reports on recent progress and updates in basic science, translational research, and clinical studies are targeted to worldwide physicians and scientists with an interest in HCT and cellular therapy.

The TCT Meetings are held in February to avoid schedule conflicts with other meetings. Five days of plenary sessions, concurrent scientific sessions, and symposia present the latest and best of basic, translational, and clinical HCT and cellular therapy research. Parallel conferences convene for nurses; center administrators; clinical research professionals, data managers, and coordinators; pharmacists; IT professionals; and others working in the field. Equally important are the ancillary meetings and collegial sharing of ideas within the transplant and cellular therapy community.

CIBMTR's Working Committees (**Chapter 6**) meet in person during the TCT Meetings to discuss ongoing studies and proposals for new studies. The TCT Meetings Scientific Organizing Committee meets during each TCT Meeting to begin planning for the next year, and the CIBMTR Advisory Committee also gathers.

Attendance at the TCT Meetings increases annually to current levels of more than 4,000registrants. A limited number of travel grants are provided for selected attendees.

The educational objectives of the TCT Meetings are to:

- Report on the state of the art in HCT and cellular therapy;
- Analyze new methods and controversial issues in clinical management strategies for reducing toxicity and improving transplant and cellular therapy outcomes;
- Assess new basic science information related to immunogenetics, molecular biology, stem cell biology, and HCT-related immunology;
- Review CIBMTR research accomplishments and set the scientific agenda for the upcoming year;
- Review accomplishments of the ASTCT, including progress on organizational, societal, and regulatory issues in HCT;
- Report on contemporary principles in HCT and cellular therapy nursing, pharmacy, data management, clinical research analysis, and center administration.

16.1.1 Relationship with the ASTCT

Holding the CIBMTR and ASTCT meetings in tandem helps reduce travel costs and schedule conflicts while also promoting networking for the 30-40% of participants who are members of both organizations. The CIBMTR and the ASTCT share the following responsibilities:

- Financial management (grant procurement and corporate support, monitoring educational exhibits, and satellite symposia);
- Agenda coordination;
- Speaker travel and reimbursement;
- Abstract submission and selection process (for oral and poster presentations);
- Strict adherence to continuing medical education and Accreditation Council for Continuing Medical Education requirements;
- Venue negotiations and contracting;
- Transportation;
- Online registration services and registration fee setting;
- Online housing services;
- Website and general logistical conference management;
- Policies regarding complimentary meeting registration and / or other compensation for selected invitees including faculty and speakers.

16.1.2 Scientific Organizing Committee

The TCT Meetings Scientific Organizing Committee is comprised of sixteen individuals who work collaboratively to select topics and speakers for the upcoming year. The CIBMTR and the ASTCT each propose six members, one fellow, and a meeting Co-Chair. The CIBMTR switches between a Co-Chair from North America and a non-North American Co-Chair every other year.

In addition to the members listed above, the following individuals participate in the committee:

- CIBMTR Chief Scientific Director;
- CIBMTR Chair of the CIBMTR Advisory Committee;
- ASTCT Executive Director;
- ASTCT President;
- ASTCT Immediate Past President;
- ASTCT President-Elect;
- ASTCT Vice President;
- NMDP/Be The Match Representative;
- Worldwide Network for Blood and Marrow Transplantation (WBMT) Representative;
- Pediatric BMT Program Representative
- Representative from each Parallel Conference.

Other committee members may be appointed by the CIBMTR Executive Committee to represent both US and non-US CIBMTR-participating centers. Other representatives may be nominated by the ASTCT President and confirmed by the ASTCT Board of Directors. Committee members are chosen to represent a wide spectrum of clinical and laboratory science interests.

This Scientific Organizing Committee meets at the conclusion of the TCT Meetings. After making its recommendations for the upcoming meetings, the TCT Meetings Manager, CIBMTR Director

of Advancement, and ASTCT staff and leadership meet during the year to coordinate planning and scheduling details.

16.1.3 CIBMTR Working Committee Meetings

All conference registrants are encouraged to attend and actively participate in the meetings of the 15 CIBMTR Working Committees (**Chapter 2 and Chapter 6**), which are scheduled throughout the TCT Meetings. During these meetings, leadership and members of each Working Committee review the past year's research accomplishments, discuss current studies, review new proposals, and establish priorities by setting the scientific agenda for the coming year. This is the only time the Working Committees meet in person, and these sessions are a core activity of the annual scientific meeting.

16.1.4 Scientific Sessions (Plenary and Concurrent)

Working Committee meetings are planned to avoid conflict with scientific sessions. At these scientific sessions, leading authorities from around the world present the latest developments in the broad field of blood and marrow transplantation and cellular therapy in plenary and concurrent scientific sessions. Topics include (among others):

- Approaches to HCT;
- Basic science and biology of hematopoietic cell engraftment;
- GVHD;
- Best treatment practices;
- Cellular therapies;
- Graft sources;
- Disease-specific issues;
- Relapse;
- Transplantation for autoimmune disease;
- HSR.

16.1.5 Symposia

Popular symposia sessions are held during mealtimes to minimize conflict with other scientific or Working Committee meetings. The symposia topics, chairs, and speakers are submitted to a subcommittee of the TCT Meetings Scientific Organizing Committee by third party Medical Education Companies. An annotated list of proposed symposia topics and an application form is published on the CIBMTR and ASTCT websites and circulated to health care companies.

Funding is provided by industry to support symposia and a variety of presentations; however, symposia are structured so that scientific and educational content are separated from commercial interests and comply with rules and guidelines for continuing medical education. A competitive bidding process ensures:

- Separation between symposia content and financial support;
- Transparency in the development of symposia content and faculty selection;
- Uniformity in symposia design, planning, execution, and outcomes assessment;
- Simplified and economical processes for companies wanting to support symposia.

16.1.6 Parallel and Ancillary Meetings

Parallel conferences and workshops are held concurrently during the TCT Meetings, with specialized sessions for nurses, clinical research professionals (data management), mid-level practitioners, pharmacists, center administrative directors, medical directors, BMT CTN coordinators and investigators, IT professionals, and pediatric cancer specialists.

Other HCT and cellular therapy-related societies and associations often hold annual board and training meetings during the TCT Meetings. Examples include NMDP/Be The Match, FACT, WBMT, Canadian Bone Marrow Transplant Group, journal review boards, and pharmaceutical firms. These ancillary meetings must be approved to ensure lack of conflict with the scientific agenda. Typically, more than 50 ancillary meetings are held during the TCT Meetings.

16.1.7 Abstract Review and Awards

Abstracts are submitted online each year and reviewed by committee leadership to select those that will be presented as posters or orally. There are usually four abstract Review Committees, each with its own assigned topics. Committee members include volunteers with related expertise, members of the Scientific Organizing Committee, and CIBMTR and ASTCT leadership. Invitations are extended by the Chairs of the Scientific Organizing Committee.

Reviewers evaluate each abstract for its impact in the fields of HCT and cellular therapy. All research must be original and not previously reported in the medical literature or at another medical meeting. Exceptions are sometimes made for work also submitted to the ASH meeting because these meetings have overlapping abstract deadlines. Reviewers complete their review and scoring online from August through October, with final decisions made by November. Committees may review the composite scores and make final decisions by conference call.

Several hundred abstracts are submitted for consideration annually with about a quarter accepted for oral presentation; most of the rest are invited for poster presentation. Travel grants are sometimes awarded to junior investigators whose abstracts are selected for oral presentations. All accepted abstracts are posted on the CIBMTR and ASTCT websites and published in an abstract book, published as a supplement to the February issue of *Biology of Blood and Marrow Transplantation*. This enables the accepted abstracts to be indexed in the medical literature.

An Abstract Awards Committee selects three clinical abstracts and three basic science abstracts to receive Best Abstract awards. The Abstract Awards Committee includes the Review Committee Chairs and the Scientific Organizing Committee Chairs. Awards are presented orally in a Best Abstracts Session. The principal author of the top choice receives a substantial monetary prize.

In addition to the clinical and basic research abstracts, there are several special categories of abstracts for oncology nursing, pharmacy, and data management. These are reviewed separately by the organizers of those educational tracks. These abstracts are presented in special sessions and categorized separately in the abstract book and online postings.

General Guidelines to follow when selecting moderators:

- Moderators must be from different institutions.
- Include moderators who are not already moderating plenary or concurrent sessions.
- Involve people from as many different institutions as possible.

- Attempt to include fewer senior moderators whenever possible.

16.1.8 Meeting Planning and Venues

The CIBMTR Advisory Committee and ASTCT Board of Directors provide direction regarding future meeting sites. Proposed venues are evaluated based on size and location of the facility, security, and accessibility by air and ground transportation, among other considerations. Registration and housing services for the meetings are subcontracted to outside vendors. TCT Meetings planners work with vendors to negotiate conference venue contracts. A member of the MCW legal staff reviews contracts on behalf of both the ASTCT and the CIBMTR prior to signature. For information about past and upcoming meetings, view the *TCT Meetings* webpage.

16.2 NMDP/BE THE MATCH COUNCIL MEETING

NMDP/Be The Match conducts its annual international Council Meeting each fall for network center physicians and other professionals working in the field of unrelated HCT. The Council Meeting is a dynamic event in which attendees gain essential training and education on scientific and clinical advances in unrelated HCT; operational efficiencies; psychosocial implications for recipients, their families, and donors; and other health sciences research. Attendees include physicians, transplant and donor center coordinators and data managers, apheresis and collection center coordinators, cord blood bank staff, and international registry staff. The Council Meeting provides networking opportunities and best practice idea sharing among colleagues in many related fields. Several other meetings are held immediately prior to, concurrent with, or after Council, including the World Marrow Donor Association Meeting and specialty meetings of interested subgroups. For more information, view the *NMDP/Be The Match* website.

16.3 OTHER MEETINGS

The CIBMTR participates in a variety of meetings to promote communication, team building, continuing education, staff training, etc. Some of the meetings in which the CIBMTR participates include:

- AcademyHealth Annual Research Meeting;
- Advanced Placement Program (AP®) Statistics Conference;
- American Society for Histocompatibility and Immunogenetics (ASHI) Annual Meeting;
- American Society of Clinical Oncology (ASCO) Annual Meeting;
- American Society of Hematology (ASH) Annual Meeting;
- Asia-Pacific Blood and Marrow Transplantation Group (APBMT) Annual Conference;
- Association of American Cancer Institutes and Cancer Center Administrators Forum;
- Brazilian Society of BMT Meeting;
- Center-Specific Outcomes Analysis Forum;
- CIBMTR Cellular Therapy Registry Forum;
- Cord Blood Connect;
- EBMT Annual Meeting;
- European Federation for Immunogenetics (EFI) Annual Meeting;
- European Immunogenetics and Histocompatibility Conference;
- European Hematology Association (EHA) Annual Meeting;

- Health Resources and Services Administration Advisory Council Meeting;
- International Conference on Malignant Lymphoma (ICML) Annual Meeting;
- International Donor Registry Conference;
- Japan Society of Hematopoietic Cell Transplantations (JSHCT) Annual Meeting;
- Latin American Bone Marrow Transplantation Group (LABMT) Meeting;
- Minnesota Developer Conference;
- Minnesota Health Services Research Conference;
- National Council of University Research Administrators (NCURA);
- Patient-Centered HCT Outcomes Research Symposium;
- Psychoneuroimmunology Research Society;
- Regenerative Medicine Forum;
- SAS Users Conference;
- Sickle Cell Disease Research and Education Symposium;
- SOCRA Chapter Meeting;
- TCT Meetings;
- University of Minnesota Bioinformatics and Computational Biology Annual Meeting;
- WBMT Meeting.

CHAPTER 17: NON-FEDERAL FUNDING

The CIBMTR raises funds to leverage its federal government funding (**Chapter 18**) to increase the organization's ability to conduct research and fulfill its mission. The CIBMTR Advancement Program Director identifies, cultivates, and solicits prospective donors. Funding is also sought from foundations for CIBMTR infrastructure support. In the same way, the CIBMTR Corporate Office Program Director is responsible for commercial partners. The objectives are to generate revenues and enhance awareness of the CIBMTR and its ongoing research initiatives.

Advancement efforts include:

- Identifying new and cultivating established individual CIBMTR donors;
- Working with CIBMTR Executive and Advisory Committee members to solicit lapsed donors and to identify new development opportunities;
- Informing and educating current CIBMTR donors and research participants about the research being conducted by the CIBMTR;
- Establishing agreements for infrastructure funding of CIBMTR major programs.

Corporate Office efforts include:

- Identifying new commercial opportunities that align with the CIBMTR's mission;
- Expanding the CIBMTR Corporate Program by soliciting newly identified pharmaceutical, biotechnology, insurance, and consulting companies and by renewing existing and lapsed relationships;
- Establishing feasible proposals and contractual agreements for infrastructure funding of CIBMTR major programs and other non-federal funding sources requiring a contract.

17.1 ROLES AND RESPONSIBILITIES

The Advancement Program Director oversees donations and membership revenue, and the Corporate Office Program Director negotiates contractual agreements with external parties interested in funding specific studies, projects, or data requests. All approved activities must comply with the policies and procedures of the MCW Grants and Contracts Office. Executed projects are under the oversight of Business Operations staff.

Staff at the NMDP/Be The Match Foundation also help raise awareness and funding for the CIBMTR. Any corporate funding secured to support CIBMTR programs, on either campus, is coordinated with the CIBMTR Corporate Office, which holds the responsibility and coordination of proposal development, contract negotiation, and budget estimation.

Tracking of deliverables for executed awards is handled by Business Operations staff, and payment schedules, invoices, and tracking of secured funds is the responsibility of the CIBMTR Business Office or NMDP/Be The Match Finance, as appropriate. All information requests from commercial companies are reviewed by the Corporate Office for determination of feasibility and implementation. Any request that requires additional contracting follows the CIBMTR Corporate Office processes.

17.2 KEY ACTIVITIES

17.2.1 CIBMTR Corporate Office

The CIBMTR Corporate Office oversees Corporate Membership (**Section 17.2.1.1**) and Corporate Studies / Projects acquisition (**Section 17.2.1.2**).

17.2.1.1 Corporate Membership

The rapidly increasing use of HCT and cellular therapies and the introduction of new technologies make frequent updates essential for information about transplant use and outcomes. The CIBMTR Corporate Membership program provides a variety of resource materials to corporations related to the most current and comprehensive data on HCT and cellular therapy. Annual Corporate Memberships help support the CIBMTR Information Request Service, which provides customized data reports describing transplantation to patients, physicians, hospitals, pharmaceutical companies, insurance companies, and others involved in healthcare.

The annual membership program provides informational materials on current trends in HCT and cellular therapy. The program includes subscriptions to the Report on Survival Statistics for Blood and Marrow Transplants, Center Volumes Dataset, US Allo HCT Activity Report, CIBMTR newsletters, and the CIBMTR Summary Slides on the state of the art in HCT. Corporate members are invited to attend CIBMTR meetings and educational forums and can access CIBMTR databases for simple analyses. These resources are useful for marketing managers, medical directors, research directors, product managers, case managers, and transplant coordinators.

There are five Corporate Membership Levels available, each described on the *CIBMTR Corporate Membership Program* webpage.

17.2.1.2 Corporate Studies and Projects

Funding can be obtained through corporate partners to support a study or project involving more complex analyses or to license a specified data set. The Corporate Office is responsible for project specification and contract negotiation. The Office coordinates with other CIBMTR operational staff members along with the Business Office staff at the applicable campus to assess feasibility of a proposal and prepare a Statement of Work and an estimated budget. Examples include:

- **Observational and Prospective Study Support.** Organizations interested in funding a study - such as one comparing HCT with one or more non-HCT therapies, one using historical controls, or a Post Authorization Safety Study - can negotiate with the CIBMTR for data and / or expert statistical analyses. Organizations wishing to submit a study proposal related to HSR should consult with the Scientific Director of the HSR program, as outlined in **Chapter 9**.
- **Prospective Trial Support.** Organizations with a small prospective trial should consult with the Scientific Director or Director of Prospective Studies with the RCI BMT (**Chapter 8**). Organizations with a prospective study involving Research Repository specimens,

laboratory, or other immunobiology tests should consult with the Director of Immunobiology Research (**Chapter 7**).

Other proposals can be directed to the Corporate Office Program Director for consideration.

17.2.2 Foundation Support

The Advancement Program Director secures funding from foundations to support specific studies or to support the infrastructure of any CIBMTR major program.

17.2.3 Individual Contributions

The CIBMTR relies on individual contributions to continue its research to seek better treatments and outcomes in HCT and cellular therapy. Contributions made to the CIBMTR are used in the following ways:

- **General Support.** The donations support the overall operations of the CIBMTR and can be applied to any of its ongoing research projects.
- **Mortimer M. Bortin Endowment.** The donations are applied to the principal of the Mortimer M. Bortin Endowment fund. Investment earnings can be used each year to support the research efforts of the CIBMTR.

17.2.4 Contracting

All proposals and budgets are evaluated on individual merits and must follow appropriate approval processes of the assigned campus. All CIBMTR approved corporate contracts, from both campuses, are documented with the Corporate Office. Contracts for proposals submitted to the RCI BMT on the Minneapolis campus must follow NMDP/Be The Match Financial standard operating procedures, and resulting contracts must include appropriate legal language. Corporate funding proposals contracted on the Milwaukee campus must be compliant with MCW Grants and Contracts policies and must include appropriate legal language.

17.2.5 Data and Publications

The CIBMTR controls all data in its databases (**Chapter 13**) and may license a portion of the data through a License Agreement with a third party. A signed Letter of Commitment for the Use of CIBMTR Datasets **(Appendix D2)** is required prior to release of any data.

The CIBMTR reserves the right to publish the results, regardless of the outcome. Contributing parties are appropriately acknowledged in any resulting publications in conformance with the provisions in the contract that funded the study.

17.3 TRANSPLANTATION AND CELLULAR THERAPY MEETINGS

The CIBMTR co-sponsors the annual TCT Meetings (**Chapter 16**) with the ASTCT, with which it shares meeting revenue and expenses. The TCT Meetings are accredited by MCW in compliance with the standards of the Accreditation Council for Continuing Medical Education. Commercial support agreements are negotiated between CIBMTR Milwaukee, the MCW Continuing Medical Education office, and the commercial supporter. The TCT Meetings include:

- **Commercially Funded Symposia.** Grants are solicited from companies to support mealtime symposia related to HCT and cellular therapy.

- **General Corporate Support.** Educational grants are solicited from companies to support various meeting activities and scientific presentations.
- **Exhibits.** Pharmaceutical and biotech companies, patient and caregiver support groups, and foundations can exhibit at the TCT Meetings for a fee.

17.4 RESPONSIBILITIES OF EACH CAMPUS

The following general guidelines are applied to foundation support and contracts with corporations. However, because each request is unique, approval must be given by the CIBMTR Chief Scientific Director, CIBMTR Advancement Program Director, CIBMTR Corporate Office Program Director, and President of the NMDP/Be The Match Foundation, as described in this section.

The CIBMTR Corporate Office Program Director in Milwaukee:

- Oversees CIBMTR Corporate Office responsibilities;
- Develops collaborative agreements with partnering organizations;
- Documents, and reports the status of, all corporate funding secured to support CIBMTR programs and research studies / projects on both campuses;
- Coordinates the commercial portfolio with Be The Match Biotherapies.

The CIBMTR Advancement Program Director in Milwaukee:

- Coordinates and solicits funding (including individual contributions) for the TCT Meetings, for donor support, and for endowments (including the Mortimer M. Bortin Endowment);
- Documents and reports the status of all meeting, donor, and endowment support.

NMDP/Be The Match Contracts and Procurement staff in Minneapolis:

- Negotiates contracts, grants, and other agreements with health care companies or other organizations that provide funding for specific BMT CTN and RCI BMT studies or CIBMTR Minneapolis research program infrastructure;
- Develops collaborative agreements with partnering organizations.
- Documents and reports the status of all agreements.

CHAPTER 18: FEDERAL FUNDING

Grants and contracts provide approximately 65% of the funds for CIBMTR activities that improve HCT and cellular therapy outcomes and patients' quality of life. This chapter describes the processes for handling federal funding. See **Chapter 17** for information about non-federal funding.

The CIBMTR facilitates all day-to-day management of financial, personnel, and operational activities for its research activities. In addition to the CIBMTR Business Office, MCW provides oversight of grants and contracts at the Milwaukee Campus, and NMDP/Be The Match Office of General Counsel, Contracts and Procurement provides oversight of grants and contracts at the Minneapolis office.

Budget approval for the CIBMTR rests with the Joint Affiliation Board (**Chapter 2**), but systems to create and administer that budget must also address the procedures and processes of the two host institutions: MCW in Milwaukee and the NMDP/Be The Match in Minneapolis. In some cases, this creates a higher level of complexity when creating budgets and expenditure reports for various entities that require an accounting, including granting organizations. This section describes how the CIBMTR manages these finances.

The CIBMTR receives funding from a wide variety of sources. The primary sources are Federal grants and contracts that are awarded to both MCW and NMDP/Be The Match. Additional sources include corporate contracts, corporate and individual gifts, service agreements, endowments, meeting revenue, and institutional support.

Because all federal grants or contracts must be received by a legal entity, CIBMTR leadership determines which entity (MCW or NMDP/Be The Match) will apply for each funding opportunity. This decision is based on several factors, including relevance to the core business, likelihood of receiving the award, and availability of appropriate leadership and project personnel. The awardee organization is the "Prime Contractor" and the other organization is the "Subcontractor."

- If MCW is the Prime Contractor, all proposals and funds are received under the umbrella of MCW on behalf of the CIBMTR and must be managed within MCW's standard operating procedures. CIBMTR staff members assigned to the contract are responsible for the contract deliverables.
- If NMDP/Be The Match is the Prime Contractor, all proposals and funds are received by NMDP/Be The Match. NMDP/Be The Match Contracts and Procurement Department staff are responsible for contract deliverables. Three-week and six-week notices are issued to the responsible parties, and all submissions are given to the NMDP/Be The Match Contracts Representative for submission.

18.1 BI-CAMPUS MANAGEMENT

18.1.1 Milwaukee Campus – MCW

MCW is a private, not-for-profit, academic institution dedicated to leadership and excellence in education, research, patient care, and service. MCW is a nationally recognized research center, the largest research institution in the Milwaukee metropolitan area and the second largest in Wisconsin. The CIBMTR is an academic division of the MCW Department of Medicine.

Financial management for CIBMTR Milwaukee is shared between the Department of Medicine and the CIBMTR. The MCW Department of Medicine also provides administrative support, if needed, to the CIBMTR for grants and accounts management, and it collaborates on the annual budgeting process.

The MCW Office of Grants and Contracts provides pre-award services, including information regarding budget preparation, the proposal submission process, and federal policies and procedures relating to grant / contract applications. It assists in contract preparation and negotiation, reviews agency budgets prior to submission of grants for processing, and accepts subcontracts from and issues subcontracts to collaborating institutions. It also serves as a liaison between granting agencies and MCW faculty.

The MCW Office of Sponsored Programs provides post-award financial oversight of projects supported by internal and external funding sources. The terms specified by the sponsor determine the level of restriction placed on the sponsored project. Grants and contracts funded on either a fixed cost or cost-reimbursement basis are assigned a unique project number to segregate financial data in the grant accounting system. For each project, the system tracks a budget, revenue, expenditures, open commitments, and the budget balance. The MCW Controller's Office sends monthly reports on each project to the PI's department. These reports include overall account status, transaction details, open commitment details, and a labor distribution listing. Sponsored Programs also generates monthly or quarterly invoices, periodic Financial Status Reports, and any other financial reports required by the sponsoring agency.

18.1.2 Minneapolis Campus – NMDP/Be The Match

The NMDP/Be The Match was established in 1986 to create and maintain a registry of volunteer donors who would consider donating hematopoietic stem cells for a patient in need of a stem cell transplant. NMDP/Be The Match is a 501(c)3 not-for-profit organization. Responsibility for financial management at NMDP/Be The Match resides with the Chief Financial Officer, and contractual management resides with the Chief Legal Officer and General Counsel.

The NMDP/Be The Match Finance / Contract and Award Accounting Department prepares and reconciles budgets, tracks actual costs incurred, and prepares invoices.

The NMDP/Be The Match Contracts and Procurement Department submits and negotiates proposals, negotiates budgets, establishes terms and conditions of contracts to ensure compliance with government and CIBMTR requirements, working within the NMDP/Be The Match Office of General Counsel to ensure compliance, and also works with NMDP/Be The Match Finance to maximize budgets and revenue.

18.1.3 Financial Relationship between MCW and NMDP/Be The Match

In 2004, a formal affiliation agreement was established between MCW and NMDP/Be The Match to create the CIBMTR (**Chapter 1**). The organizations collaborate on a variety of awards and service agreements to provide and share resources, such as staff support, patient care costs, travel funds, and other expenses.

The CIBMTR Business Office and NMDP/Be The Match Finance Department together manage the organization's finances and prepare various reports for CIBMTR leadership at each respective institution, as well as a combined CIBMTR financial report, and also to research partners and federal agencies, to aid in strategic planning.

The Joint Affiliation Board has final approval on all budget items. Voting members of the Board include the NMDP/Be The Match Chief Executive Officer, NMDP/Be The Match Chief Financial Officer, MCW Senior Associate Dean for Research, and a Controller from the MCW Office of Finance and Administration.

18.2 PROJECT BUDGETS

Contract, grant, and study budgets are prepared by the CIBMTR Business Office or NMDP/Be The Match Finance, as appropriate. Tasks include:

- **Preparing the Budget**. Preliminary and final budgets are prepared in cooperation with the Project Director and any other relevant personnel, in accordance with the sponsoring institution guidelines.
- **Determining Labor Costs**. Similar past projects are reviewed for applicable actual costs. Standard or approved Federal labor rates are applied, as applicable.
- **Assessing Travel and Meeting Expenses**. Travel expenses, which can comprise a substantial part of a project budget, are carefully estimated. Working, Advisory, and Executive Committee Chair travel stipends, as well as operational staff travel expenses, affect these travel costs.
- **Estimating Other Direct Costs**. CIBMTR Business Office staff work with MCW or NMDP/Be The Match Contracts and Purchasing to obtain cost estimates or bids from external product and service providers.
- **Determining Government or Institutional-Approved Fringe and Indirect Rates**. These rates are used for all project budgets, unless otherwise directed by management or the granting agency.

Proposed budgets must be approved by MCW or NMDP/Be The Match. Proposals are negotiated by the respective institution, supported by the scientific personnel and NMDP/Be The Match Finance or CIBMTR Business Office. MCW budget proposals are submitted by the CIBMTR Business Office to the Grants and Contracts Office via the online eBridge system. This site allows the MCW faculty and research staff to submit, track, report, and archive applications involving funding proposals as well as human subject and animal research conducted at MCW. All proposal approvals, budgets, and awards are managed through this system, including sub-awards issued and received. Upon award, the MCW Office of Sponsored Programs or NMDP/Be The Match Finance assigns unique general ledger / project account numbers to track expenses

and billing. Fee schedules for projects such as the SCTOD (**Chapter 6**) are prepared by NMDP/Be The Match Finance in collaboration with the applicable CIBMTR personnel.

18.3 INVOICING AND CONTRACT MANAGEMENT

NMDP/Be The Match and MCW invoices are prepared based on actual costs incurred and / or projections of costs (if advance invoicing is allowed) and upon the terms of the grant or contract. Invoices are issued to the appropriate agency, and NMDP/Be The Match Finance or MCW Office of Sponsored Programs tracks to ensure prompt payment. NMDP/Be The Match and MCW CIBMTR also internally track payments processed by detailed category to provide CIBMTR leadership with timely reporting of costs incurred as well as ongoing projections for the entire grant / contract period.

Any revisions or amendments to contracts are approved by CIBMTR leadership and processed with respective institutional approvals. All contracts are closed out in accordance with the terms in the contract and the relevant government regulations, and they adhere to the standard operating procedures of each institution.

CHAPTER 19: INTERNATIONAL PARTNERS

The HCT and cellular therapy field has benefited from an international collaboration of organizations that collect, analyze, and share data to address important clinical research efforts that affect the global community. Hundreds of centers worldwide submit outcome data to the CIBMTR, many since the time of its inception in 1972. The IBMTR, precursor to the CIBMTR, established research and data sharing relationships first with the European transplant groups / registries and has since developed strong collaborative relationships with other groups worldwide.

The CIBMTR often collaborates on research studies with international (and domestic) HCT and cellular therapy groups. These studies are proposed and presented to CIBMTR Working Committees by the lead researcher or group, and issues such as data sharing plans, analyses, and writing / authorship are determined early in the process. **Chapters 3, 6,** and **13** address this in more detail.

The CIBMTR is one of the four founding members of the WBMT along with the APBMT, EBMT, and the WMDA. The WBMT's mission is to promote excellence in HCT through collaboration of existing international societies using coordination, communication, and advocacy. It engages in charitable, scientific, and educational activities to promote and foster scientific and clinical disciplines, information exchange, and recipient and donor research relating to HCT and cellular therapy. Learn more about the WBMT and its 24 Member Societies on the *WBMT* website.

In addition to the Member Societies of the WBMT, the CIBMTR has longstanding, collaborative relationships with many other international organizations (**Table 19.1**).

Table 19.1: International Organizations with which the CIBMTR Collaborates

Organization	Description
AABB *aabb.org*	AABB, formerly known as the American Association of Blood Banks, is an international non-profit association committed to advancing the practice and standards of transfusion medicine and cellular therapies to optimize patient and donor care and safety.
African Blood and Marrow Transplantation Group **(AFBMT)** afbmt.org	AFBMT represents transplantation programs and activity on the entire African continent; formed in December 2014, it is now organized with officers and bylaws. It currently reports activity data to the WBMT; however, long term goals include transplant outcomes reporting.
American Society for Apheresis **(ASFA)** *apheresis.org*	ASFA is an organization of physicians, scientists, and allied health professionals whose mission is to advance apheresis medicine for patients, donors, and practitioners through education, evidence-based practice, research, and advocacy.

Organization	Description
American Society for Transplantation and Cellular Therapy **(ASTCT)** *asbmt.org*	The ASTCT is an international association that promotes the advancement of the cellular therapy field by representing the interests of transplant clinicians and investigators and the patients they serve.
American Society of Hematology **(ASH)** *hematology.org*	With more than 17,000 members from nearly 100 countries, ASH is the world's largest professional society serving both clinicians and scientists around the work working to conquer blood diseases.
American Society for Histocompatibility and Immunogenetics **(ASHI)** *ashi-hla.org*	ASHI is a non-profit association of clinical and research professionals that is dedicated to advancing the science and application of histocompatibility and immunogenetics and advocating the highest standards of laboratory testing in the interest of optimal patient care.
Asia-Pacific Blood and Marrow Transplantation Group **(APBMT)** *apbmt.org*	APBMT is an international organization of HCT and cellular therapy researchers that allows physicians in Asian countries involved in the field to share their experience and develop cooperative studies.
Australasian Bone Marrow Transplant Recipient Registry **(ABMTRR)** *abmtrr.org*	ABMTRR promotes HCT and cellular therapy research and helps provide access to and information about the field to people in Australia and New Zealand.
Eastern Mediterranean Blood and Marrow Transplantation **(EMBMT)** *embmt.org*	EMBMT promotes all aspects of patient care, academic, and research activities associated with HCT in eastern Mediterranean countries with the goal of sharing experience, initiating cooperative trials, and establishing common strategies to advance the field.
Eurocord *eurocord-ed.org*	Eurocord promotes national and international collaborations and disseminates HCT knowledge. The Eurocord registry operates on behalf of the EBMT, and Eurocord works in close collaboration with cord blood banks and EBMT centers and database.
European Federation for Immunogenetics **(EFI)** *efiweb.eu*	EFI aims to promote research in immunogenetics, histocompatibility testing, and HCT. It promotes the advancement of immunogenetics in Europe and supports research and training in the field.

Organization	Description
European Society for Blood and Marrow Transplantation **(EBMT)** *ebmt.org*	EBMT aims to improve outcomes of HCT and cellular therapy and provide information to the public about developments in the field by sharing the experience of European centers and encouraging cooperative research among scientists and physicians in the field.
European Leukemia Network **(ELN)** *leukemia-net.org*	The European Leukemia Network is a research network of 194 participating centers in 39 countries all cooperating in the Network. The goal is a cure of leukemia by integration of European leukemia research. The website delivers information (in various European languages) for physicians, patients (e.g. patient organizations in Europe), ongoing clinical trials and further information about leukemia.
European Marrow Donor Information System **(EMDIS)** *emdis.net*	The EMDIS system integrates the national blood and marrow donor registries worldwide, automating all search and business processes between the national databases and networks.
European School of Haematology **(ESH)** *esh.org*	ESH is a non-profit institution for continuing education that promotes and facilitates access to research in hematology and related disciplines in Europe, North America, North Africa, and the Middle East. ESH also develops tools for continuing education produced in collaboration with international experts in the field.
Foundation for the Accreditation of Cellular Therapy **(FACT)** *factwebsite.org*	FACT is a non-profit organization that establishes standards for high-quality medical and laboratory practices in cellular therapy for the purposes of voluntary inspection.

Organization	Description
International Cellular Therapy Coding and Labeling Advisory Group **(ICCBBA)** *iccbba.org/*	ICCBBA is a not-for-profit, tax exempt, non-government organization responsible for management of the ISBT 128 Information Standard for Blood and Transplantation, a global standard for the terminology, identification, labeling, and information transfer of human blood, cell, tissue, and organ products across international borders and disparate health care systems. It ensures the highest levels of accuracy, safety, and efficiency for the benefit of donors, patients, and ISBT 128 licensed facilities worldwide. The system features a unique, highly flexible, and comprehensive coding method for every collected product and provides international consistency to support the transfer, transfusion, or transplantation of blood, cells, tissues, and organs.
International Society of Blood Transfusion **(ISBT)** *isbtweb.org*	ISBT is an international professional society that facilitates knowledge about transfusion and transplantation science and medicine.
International Society of Cellular Therapy **(ISCT)** *isctglobal.org*	ISCT is a global association that promotes cellular therapy research by fostering international translational research, driving commercialization strategies, and providing education.
Japan Society for Hematopoietic Stem Cell Transplantation **(JSHCT)** jshct.com	Primarily an academic society for transplant clinicians, JSHCT recently expanded its interests to cellular therapy and regenerative medicine. JSHCT members play key roles in steering the Japan Marrow Donor Program, Japan Cord Blood Bank Network, APBMT , and WBMT.
Joint Accreditation Committee – ISCT (Europe) & EBMT **(JACIE)** *jacie.org*	JACIE is a non-profit organization that assesses and provides accreditation in the field of cellular therapy. Its primary aim is to promote high-quality patient care and laboratory performance in HCT collection, processing, and transplantation through an internationally recognized system of accreditation. It partners with EBMT, ISCT, and FACT.

Organization	Description
Latin American Bone Marrow Transplantation group **(LABMT)** *wbmt.org*	The purpose of this group is to provide a mechanism through which Latin American HCT and hematology groups can collaborate and engage in scientific and educational activities and endeavors to promote excellence in stem cell transplantation, stem cell donation, cellular therapy, and hematologic practices. Activities include data collection and sharing outcome information.
World Marrow Donor Association **(WMDA)** *worldmarrow.org*	WMDA is a global association whose mission is to assure that high-quality stem cell products are available for all patients in need, while maintaining the health and safety of volunteer donors. WMDA now incorporates all functions previously undertaken by Bone Marrow Donors Worldwide and Netcord.

APPENDIX A: GLOSSARY / ACRONYMS

Term / Abbreviation	Definition
ABMTR	Autologous Blood and Marrow Transplant Registry
ABMTRR	Australasian Bone Marrow Transplant Recipient Registry
AFBMT	African Blood and Marrow Transplantation Group
AGNIS	A Growable Network Information System
APBMT	Asia-Pacific Blood and Marrow Transplantation Group
ASHI	American Society for Histocompatibility and Immunogenetics
ASFA	American Society for Apheresis
ASH	American Society of Hematology
ASTCT	American Society for Transplantation and Cellular Therapy
BMDW	Bone Marrow Donors Worldwide
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
caDSR	Cancer Data Standards Registry and Repository
CDC	Centers for Disease Control and Prevention
CDE	common data elements
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CIDR	Cellular Immunotherapy Data Resource
CIT	CIBMTR Information Technology group
COR	Contracting Officer's Representative
CPA	Center Performance Analytics
CPI	continuous process improvement
CRC	Clinical Research Coordinator
CRF	Comprehensive Report Forms
CRID	CIBMTR Recipient ID Assignment
CTED	Cellular Therapy Essential Data
CVDR	Center Volume Data Report
DBtC	Data Back to Center

Term / Abbreviation	Definition
DCC	Data and Coordinating Center (of the Blood and Marrow Transplant Clinical Trials Network)
DISCO	Data and Information for Coordinating Center Operations
DKMS	German Bone Marrow Donor Center (Deutsche Knochenmarkspenderdatei GmbH)
DSMB	Data Safety Monitoring Board
DUA	Data Use Agreement
EBMT	European Society for Blood and Marrow Transplantation
eDBtC	Enhanced Data Back to Center
EFI	European Federation for Immunogenetics
EHA	European Hematology Association
ELN	European Leukemia Network
EMBMT	Eastern Mediterranean Blood and Marrow Transplantation
EMDIS	European Marrow Donor Information System
ePRO	Electronic Patient Reported Outcomes
ESH	European School of Haematology
ETL	Extract, Transform, and Load
FACT	Foundation for Accreditation of Cellular Therapy
FDA	Federal Drug Administration
GVHD	graft-versus-host disease
HCT	hematopoietic stem cell transplantation
HIPAA	Health Insurance Portability and Accountability Act
HLA	human leukocyte antigen
HRPP	Human Research Protection Program
HRSA	Health Resources and Services Administration
HSR	health services research
IBMTR	International Blood and Marrow Transplant Registry
ICCBBA	International Cellular Therapy Coding and Labeling Advisory Group
ICML	International Conference on Malignant Lymphoma

Term / Abbreviation	Definition
IDW	Integrated Data Warehouse
IRB	Institutional Review Board
ISBT	International Society of Blood Transfusion
ISCT	International Society of Cellular Therapy
ISSO	Information Systems Security Officer
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information Technology
JACIE	Joint Accreditation Committee-ISCT (Europe) & EBMT
JAMA	The Journal of the American Medical Association
KIR	killer-cell immunoglobulin-like receptors
LABMT	Latin American Bone Marrow Transplantation group
MCW	Medical College of Wisconsin
MHC	major histocompatibility complex
MiHAs	minor histocompatibility antigens
MS	Master of Science (-level Statistician)
NCI	National Cancer Institute
NCBI	National Center for Biotechnology
NGS	next generation sequencing
NHLBI	National Heart, Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIHMS	National Institutes of Health Manuscript Submission
NIST	National Institute of Standards and Technology
NMDP	National Marrow Donor Program
OHRP	Office of Human Research Protection
OIT	Office of Information Technology
OMB	Office of Management and Budget
PBSC	peripheral blood stem cell

Term / Abbreviation	Definition
PCORI	Patient Centered Outcomes Research institute
PI	Principal Investigator
PII	personally identifiable information
PL/SQL	Procedural Language / Structure Query Language
PMCID	PubMed Central Identification
POA&M	plan of action and milestones
RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
RDB	Research Database
RFI	Request for Information
SCAP	Security Content Automation Protocol
SCTOD	Stem Cell Therapeutic Outcomes Database
SPORT	Security and Privacy Online Reporting Tool
SSP	System Security Plan
TCSA	Transplant Center Specific Analysis
TCT	Transplantation and Cellular Therapy
TED	Transplant Essential Data
US	United States
WBMT	Worldwide Network for Blood and Marrow Transplantation
WMDA	World Marrow Donor Association

APPENDIX B: GUIDELINES FOR CIBMTR STUDY PRINCIPAL INVESTIGATORS

The role of a Study Chair / PI is to behave ethically and do whatever it takes to complete the study that answers your research question. It is easier to accomplish this task if you have an understanding of the CIBMTR study process, specifically where and when your efforts are most needed. The following document will explain the life-cycle of a CIBMTR observational study and review the responsibilities of a PI. Hints and tips to make the study process as successful as possible are noted with an arrow (→).

STUDY PROPOSAL

The PI is usually the first person who suggests the study and who prepares the *Study Proposal*. Ideally the PI presents his or her proposal in person to the appropriate Working Committee at the TCT Meetings. Some PIs view the CIBMTR presentation as a formality but, in reality, it is an important opportunity to convince the other Working Committee members that your study is more important, more feasible, and more likely to advance the field and be published in a high-profile journal than other studies being proposed. CIBMTR Working Committee hours and resources are limited, and not all good studies proposed can be supported.

→ Please look at the data collection forms prior to preparing your proposal. Many people propose studies that require data not collected routinely by the CIBMTR. Studies that require additional data collection usually get greater scrutiny because of the extra time and effort required whenever centers have to be contacted for additional data. Additionally, the response rate to requests for supplemental data is often disappointing – ask your own data managers how difficult it is to go back and find data for patients transplanted years ago. The ability to collect supplemental data successfully depends on how complex and / or extensive the data are, the size of the study population, how far back in time the transplants were done, and whether you have resources (people or funds) to assist in the process.

Note that study proposals may be submitted *throughout the year*. The vast majority are submitted just before the deadline, three months before the TCT Meetings. If you want your proposal to benefit from greater CIBMTR statistical and scientific input, then submitting your proposal far in advance is helpful. Proposals submitted throughout the year will be reviewed by the Working Committee Chairs and Scientific Director. They have the authority to approve a proposal based on the importance of the scientific question or they may elect to defer it until presentation at the Working Committee meeting.

PRIORITIZATION AND DISTRIBUTION OF STATISTICAL HOURS

After the TCT Meetings, the Working Committee Chairs, Scientific Directors, and Statistical Staff meet to discuss the results of the meeting and prioritize new and ongoing studies. Studies are assigned Coordinating Center hours according to their need and priority. In general, a study needs 100 hours of Statistical Staff time to finish the protocol document, 100-140 hours to prepare the data file (depending on whether additional data collection, follow-up, or excessive data cleaning is necessary), 60 hours for the analysis phase, and 50 hours for manuscript preparation. PIs are generally notified about Committee decisions (i.e., approval, prioritization, and assigned hours) regarding their proposals within one month after the meeting and after final Advisory Committee approval of the complete research agenda. At that time, the Working Committee Statistician serves as the point person for communications.

→ PIs can increase the chance of their proposal being approved by carefully preparing the Proposal Form that is presented to the Working Committee. Discussion with CIBMTR Statistical Staff and Working Committee Chairs in advance of the Working Committee meeting may help clarify the study and address study design questions. Many great concepts fail because PIs do not consider available data, size of the available study population, power calculations, and other statistical issues. The Working Committee is much less receptive to studies that appear to have multiple unresolved issues at the meeting.

STUDY PROTOCOL

The next step in the study's life is generation of the study protocol. This is an important document that is first drafted by the PI and submitted to the MS-level Statistician. The draft study protocol should be completed by the date specified by the Coordinating Center in the "Letter of Commitment". In preparing this document, it is crucial to carefully consider the variables to be included in the analysis, because the MS-level Statisticians and Scientific Directors use these documents to guide data collection and cleaning. Common pitfalls include failure to include important variables to address study hypotheses and failure to consider potentially confounding variables. After the initial draft is reviewed and approved by the Coordinating Center, it is circulated to the Working Committee for comment; at that time, Committee members may request to participate in the study and a Writing Committee is formed (see below). Individuals wishing to serve on the Writing Committee provide substantive comments on the study protocol. It is the PI's responsibility to collate and address these comments by either modifying the protocol or providing an explanation for not incorporating suggested changes. Since Writing Committee members earn their authorship by reviewing the study protocol, analyses, and manuscripts, the CIBMTR also keeps track of comments and contributions.

→ Each study protocol is reviewed at the weekly Coordinating Center conference call / meeting (held on Tuesdays, 9:30-10:30 am US Central Time) before distribution to the Working Committee; it is very helpful for the PI to join that meeting by phone and to participate in the discussion of the study's design and implementation. (Studies are again discussed at a Coordinating Center weekly meeting as they reach significant milestones. PI participation in each of these discussions is strongly encouraged.)

→ The most successful PIs respond to Writing Committee critiques as they do journal reviews — by carefully organizing them and responding to each. If a Writing Committee member brought up an issue, it is likely that a reviewer will also bring up the same points. It is expected that the PI will summarize and respond to these critiques within three weeks after the deadline for comments has passed.

→ PIs have a great deal of control over the time between study proposal approval and the completion of a final study protocol. Timely submission of the draft protocol and response to Writing Committee comments can vault your study ahead of others in terms of Coordinating Center priority. If yours is ready to go and another is not, yours may be given priority, even if initially it was planned for the other study to be done first.

DATA COLLECTION

If supplemental data collection is needed for the study, approval from the Chief Scientific Director is required. The PI needs to provide the following information for the approval: 1) number of questions, 2) types of questions, 3) number of cases and 4) the study calendar. Once the request has been approved, the "Forms Development CRC" will prepare a supplemental form for review within one week. This draft form will be a Word document listing all the supplemental questions that are relevant, as well as the most frequent response options. This form will have input from the Scientific Director, PI, Study Statistician, Metadata and Data Operations Staff for clarity, length, internal consistency of response options, and feasibility of data retrieval. The form will be formatted to be consistent with other CIBMTR forms, and a table will be created in the database to receive the data. This step is very important for any study collecting additional data. If the form is long or leaves out critical variables, the ultimate study results could be compromised by missing data. The supplemental form will go to the Chief Scientific Director, Scientific Director and PI for final approval. The Scientific Director and PI will prepare a letter detailing the importance of the data needed for the study with a copy to the Medical Director. This letter will be sent with the study request. If terms or concepts on the supplemental data collection form are unfamiliar to the data management teams, an instruction manual that describes the variable and provides examples of how data managers should interpret primary data will have to be written. Each study is assigned a CRC who communicates with centers to facilitate data submission. Most, but not all, centers are very responsive to these requests. If some centers are lagging behind in submitting extra forms, PIs may need to make personal email or phone appeals.

→ Providing the initial draft form and content for the instruction manual is the responsibility of the PI. Delay in putting it together can significantly delay initiating the data collection process. If the process is inordinately delayed so that the data needed for a study is not available in a timely manner, the study may be deferred to the next year.

→ For smaller studies, where every patient counts, personal appeals from the PI to the Transplant Center Director can sometimes be very effective.

DATA FILE PREPARATION

In this step, the MS-level Statistician prepares a data file using the finalized study protocol as guidance. Data interpretation issues may arise here, especially if uncommon variables are necessary for the study. Values for common variables have probably already been reviewed and, if missing or out of range or inconsistent, already clarified (data "cleaning") for other studies. If your study is the first to examine a particular variable or study population, then expect to do a lot of data cleaning.

→ The PI can accelerate this process by being available to the MS-level Statistician and Scientific Director as questions come up. The PI should also carefully review the frequencies of study variables for outliers and other clinical inconsistencies.

UNIVARIATE ANALYSIS

Once the data file is prepared, the MS-level Statistician performs as much of the analysis as possible before handing the data set to the Statistical Director assigned to the project. First, a table of study population characteristics and preliminary univariate analysis is prepared. This is

reviewed by the PI and Scientific Director. When they are satisfied with the population, the study is scheduled for another Coordinating Center weekly meeting / conference call to confirm final composition of the population and study design and review the univariate analysis before multivariate analyses are performed. Relevant comments from the Coordinating Center review will be summarized by the MS-level Statistician and the Scientific Director and relayed back to the PI for comment if the PI cannot participate personally in the meeting.

→ As noted above, the PI is invited to participate in the CIBMTR Coordinating Center Meeting (Tuesdays) when his or her study is discussed. It is worth repeating that it is very helpful for the PI to participate since they can often address questions as they arise so that the statistical input is most helpful.

MULTIVARIATE ANALYSIS

Once the population characteristics and univariate analyses are approved, the data file is transmitted to the Statistical Directors for multivariate and more complex modeling. When completed, results are sent to the PI and Scientific Director who prepare a memo for circulation to the Writing Committee for comments after review at the weekly statistical meeting. The comment period usually lasts two to three weeks. The PI summarizes the comments and prepares another memo for the Writing Committee within three weeks of the close of the comment period. If substantive issues arise, especially related to the study population or analyses, then a conference call involving the PI, Scientific Director and Statisticians may need to be convened to plan an approach for addressing the comments.

→ The most successful PIs take advantage of the MS-level Statisticians' and Statistical Directors' familiarity with the project and the data to finish their analyses quickly. If extended time passes between each phase of the analysis, the Statisticians will need to re-familiarize themselves with the project and coding. A task that could take a couple of hours immediately after the initial results are completed may take much longer a month or two later (and the Statisticians understandably will be less excited about picking up the project again).

ABSTRACTS

Many PIs hope to submit abstracts to national and international meetings. Multivariate analyses must be complete with enough time to allow generation of an abstract. These abstracts must be circulated to the Writing Committee and reviewed by the Coordinating Center staff prior to submission. Please allow enough time to complete these steps before the abstract deadline. If the abstract is accepted for oral presentation, the Coordinating Center staff will also need to review the slides, primarily for accuracy but sometimes also to make suggestions for clarity. The CIBMTR has a template for format and background that is required for all presentations.

→ Planning for ASH and other meeting abstracts happens immediately after the TCT Meetings. If you would like to submit your abstract to one of these meetings, an early declaration of your intentions and demonstrable effort in moving towards that goal will result in your study getting higher priority.

→ In general, studies are only submitted to one meeting; once submitted in abstract form, priority should be placed on writing and submitting the manuscript.

→ Submission of abstracts should not delay preparation of manuscripts. PIs are expected to meet manuscript preparation deadlines independently of abstract submission.

MANUSCRIPT

Once the analysis is completed, drafting the manuscript is the responsibility of the PI. A draft manuscript is expected within 30 days of the final analysis. The draft is circulated to the Writing Committee and comments are again summarized and incorporated. At least one round and sometimes up to three or more rounds are necessary to create a final manuscript. The CIBMTR will do the final formatting for journal submission, attach all the co-authors' information (such as institution and contact information), collect any necessary signatures, and submit the paper. The CIBMTR has a long list of acknowledgment for funding sources that are usually attached to the paper.

→ The initial manuscript draft usually causes the greatest delay in study progress and is the step most directly under control of the PI. The most successful PIs recognize that publishing their study results is a critical measure of success for all involved parties - themselves, the CIBMTR and all the collaborators involved in the study. Working Committee Chairs have the authority to re-assign a study to a different PI if the delay in manuscript preparation is too long (>60 days).

ACCEPTANCE

Unless the paper is accepted on the first submission, it will need to be revised or resubmitted. If comments are straightforward, the PI can prepare a response to reviewers for circulation, along with the revised version. Some comments from reviewers require additional analyses or discussion at a Coordinating Center meeting prior to resubmission. The CIBMTR will assist with manuscript resubmission. Once the paper is accepted, the PI also handles proof review.

→ Unless a study is completed in record time, it will be "in progress" at the next TCT Meetings. PIs should plan to present a study update at the CIBMTR Working Committee meetings or designate another person on the Writing Committee to do this, as long as the study is active.

→ Any expected or unexpected deviations from the above timetable should be discussed between the PI and the Scientific Director. Sometimes unavoidable delays are due to either the CIBMTR or the PI. A proactive plan designed to keep the study moving forward should be devised. Generally, the CIBMTR expects studies to be completed within 18-24 months.

APPENDIX C: GUIDELINES FOR ACQUIRING PUBMED CENTRAL IDENTIFICATION (PMCID) NUMBERS

All publications funded by the NIH must comply with the *NIH Public Access Policy*. This policy, which applies to any NIH-funded (including all agencies under the NIH), peer-reviewed material accepted on or after April 7, 2008, requires acquisition of a PubMed Central Identification (PMCID) number. This includes data supported by the NCI, the NHLBI, and the NIAID. The *NIH* website has a complete list of all agencies that are under it.

The PMCID is a unique number assigned to a work that is posted to *PubMed Central*, a free digital archive of biomedical and life sciences journal literature at the NIH, developed and managed by NIH's National Center for Biotechnology Information in the National Library of Medicine. All works applicable under the NIH Public Access Policy are posted to PubMed Central.

NIHMS facilitates submission of final, peer-reviewed manuscripts online. When a manuscript is accepted, most but not all journals will then submit the paper to NIHMS. If the journal does not provide this service, the corresponding author or another designated individual, must do so. If they are unable to do so, then the CIBMTR must complete this. View the *NIH* website for more information.

When the manuscript is accepted by NIHMS, a NIHMS identification number is assigned and the following three steps occur:

- **Approve PDF Receipt**: A PDF version is sent to the Corresponding Author to verify that the correct manuscript was submitted. The NIHMS email subject line is "Approve PDF Receipt" (email displays NIHMS #). The Corresponding Author must approve the PDF.
- **Undergoing NIHMS submission review and file preparation / Undergoing conversion to PMC documents**: The PDF version that was approved is being converted into the final web version.
- **Approve Web Version**: A second mailing is sent to the Corresponding Author asking to "Approve Web Version." The PMCID assignment is contingent on final approval of this web version by the Corresponding Author.

The CIBMTR employs two methods for submitting manuscripts to a journal to ensure compliance with PMCID requirements:

- The CIBMTR submits the manuscript (preferred);
- Principal Investigator / corresponding author submits the manuscript.

If a Principal Investigator / corresponding author prefers submitting his / her own manuscript, CIBMTR requests that he / she follow the guidelines outlined below and in **Chapter 4** to inform the Coordinating Center that a paper has been submitted on behalf of the CIBMTR. In either case, the **designated reviewer is responsible for the required interactions** with NIHMS after paper is accepted.

The following documents should be included with manuscript submissions:

- A CIBMTR "Data Sources Statement" (**Appendix F**);

- A current "CIBMTR Support List" (**Appendix G**);
- Acknowledgement of NIH funding if applicable (e.g., "CIBMTR NIH Support Verification Letter") (**Appendix H**).

When the journal asks if the manuscript and / or data are NIH-funded, respond "yes if applicable".

The proper CIBMTR grant number is **U24-CA76518**-[current funding cycle year]. For example, U24-CA76518-14.

When a manuscript is accepted, most but not all journals will then submit the paper to NIHMS. If the journal does not provide this service, the Corresponding Author or the CIBMTR must do so. View the *NIH* website for more information.

APPENDIX D1: LETTER OF COMMITMENT TO COMPLETE CIBMTR OBSERVATIONAL STUDIES

Date

PI's name
PI's address
PI's address

Re: **PRINCIPAL INVESTIGATOR (PI) COMMITMENT TO COMPLETE A CIBMTR OBSERVATIONAL STUDY**
CIBMTR *study # and title*

Dear Dr. *PI's last name*:

Congratulations on the approval of your proposal as a CIBMTR study. The commitment and expertise of Principal Investigators (PIs), like you, is vital to our ability to conduct the highest quality scientific analyses. The study process, and preparation of a study dataset in particular, are rigorous, so it is critical for PIs to work closely with CIBMTR scientific and statistical staff to successfully complete their projects in a timely fashion. We recognize that you are likely to commit a substantial amount of time to this project, and we will support your efforts.

Please review the following list of PI expectations. We will begin the study or dataset preparation process after we receive your acknowledgement and acceptance of these responsibilities:

- Read the CIBMTR Guidelines for Principal Investigators.
- Read the CIBMTR Guidelines for acquiring PubMed Central Numbers (PMCID).
- Assist the Working Committee Chairs and Coordinating Center staff in developing a reasonable timeline for study completion.
- Prepare a first Draft Study Protocol by *Date* of this year.
- Prepare the Final Study Protocol (having given consideration to all Writing Committee comments) within 30 days of distribution date to full Working Committee (CIBMTR will remind you 14 days in advance).
- Participate actively in teleconferences and meetings (e.g., weekly Statistical Staff meetings upon invitation).
- Participate actively in data file preparation and analyses.
- Prepare a first draft of the manuscript within 30 days of receiving the final study results.
- Prepare any subsequent manuscript draft within 30 days of prior distribution to Writing Committee.

- Prepare study materials, as necessary, for submission for meeting presentation.
- Collate and prepare memos addressing comments of Writing Committee members at protocol, analyses and manuscript stages.
- Collaborate with CIBMTR Coordinating Center in submitting the manuscript, or submit per CIBMTR guidelines.
- Submit a "CIBMTR Conflict of Interest Disclosure Form" **(Appendix E)** to the CIBMTR Coordinating Center;
- Address comments from reviewers, with input from CIBMTR Working Committee leadership and other co-authors.
- Respond to editorial questions and approve galley proofs.

If you are unable to meet the responsibilities outlined above, Working Committee leadership or a member of the Coordinating Center staff may assign your role to someone else and/or decline to credit your participation in the finished product. These consequences are unlikely, as most PI's successfully fulfill their responsibilities; however, it is essential that you complete activities in a timely fashion.

By signing this Letter of Commitment, you state that you clearly understand your responsibilities, and you agree to optimize this opportunity to complete a high-quality study in a timely manner. Please know that CIBMTR values your role and is prepared to support your efforts.

Please return this signed *Letter of Commitment* by the deadline noted in the accompanying email message (includes co-PIs).

I certify that I have read this document and commit to fulfilling the responsibilities described herein.

Agreed by:

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

_____

Study Number

PLEASE FAX SIGNED FORM TO CIBMTR MILWAUKEE CAMPUS: 414-805-0714
(If you wish to scan, send to *contactus@cibmtr.org*)

APPENDIX D2: LETTER OF COMMITMENT FOR THE USE OF CIBMTR DATASETS

Date

PI's name
PI's address
PI's address

Re: **PRINCIPAL INVESTIGATOR COMMITMENT FOR THE USE OF CIBMTR DATASETS**
CIBMTR request # and title [protocol or proposal must be attached]

Dear Dr. PI's last name:

The Principal Investigator (PI) requirements for use of CIBMTR datasets are outlined below. This signed agreement must be received before data for the referenced protocol/proposal will be released by the CIBMTR Coordinating Center. The data will be provided to you as a de-identified dataset; under no circumstances will the CIBMTR release the key to patient or center identity to you or any other member of the research team. CIBMTR is committed to public use of its data for the advancement of patient care and scientific debate. CIBMTR is also obligated to protect the privacy and confidentiality of human subjects as well as the rights of those who have submitted and assembled the data. We appreciate your support of those commitments.

Before receiving data from the CIBMTR, we require that you:

- **Clearly describe any anticipated proprietary use of the data or the work product that derives from use of the data.** Any proprietary uses of the data will require approval from CIBMTR prior to the release of data. CIBMTR strives to make knowledge derived from its data available for use in the public domain. This relates in part to collection of data through U.S. Governmental financial support and its underlying philosophy of making both data and study results available for the betterment of patients and science.
- **Agree to not sell information derived from the data,** unless express written permission has been received from CIBMTR.
- **Ensure protection of the data.** If accessing the data from a remote location on a time-sharing Network, computer system, or local area network with any statistical package, you will not share with any other individual(s) any logon name or password provided by CIBMTR.
- **Agree that the data are private and confidential** and that you will have in place and shall maintain administrative, technical, procedural, and physical safeguards sufficient to protect the confidentiality of the data, including preventing unauthorized access and use.

- **Agree to neither use nor permit others to use or to link the data** other than for the CIBMTR approved project for which it was intended. Prior to implementation of any change in the intended use of the data, a request for change must be submitted to CIBMTR and approved in writing as an amendment to this agreement.
- **Agree to not use or permit others to use or to link the data** to identify individuals, or to combine the data with other patient-level information.
- **Agree to not make copies of the data. Agree to neither release nor permit others to release the files or data** therein to any person (including media and subcontractors) except with the written approval of CIBMTR in order to accomplish the study goals.
- **Certify that you are responsible** for ensuring that only staff with a "need to know" shall access the data and that any support staff assigned to this project and having access to these data will likewise follow these provisions.
- **Agree to provide a status report to CIBMTR** one year after delivery of the dataset and annually thereafter, or upon request from the CIBMTR, until the approved use of the data has been completed; this report will describe the status of the project approved for the use of these data.
- **Agree that all data will be destroyed or returned to CIBMTR** as of (provide date): _____ or upon completion of the approved use, whichever comes first; user will certify in writing to the CIBMTR such destruction of all copies, including archival copies of the data.
- **Agree to comply with all applicable laws and regulation with regard to use of the data,** including but not limited to obtaining and maintaining appropriate local IRB oversight consistent with the uses of the data where applicable. Documentation of IRB review (or documentation by the relevant IRB as to why review was deemed unnecessary under applicable regulation) must be provided to CIBMTR prior to release of the dataset to the investigator. Any publication deriving from these data must contain a statement confirming the study was conducted in accordance with all applicable human subjects' protections laws and regulations.
- **Agree to notify CIBMTR of any change in employment and request from CIBMTR an amended agreement with the new institution before changing the location and responsibility for the data.**

If the intent is for publication and results will include clinical interpretation or conclusions, CIBMTR will require the following:

- All data, a description of the methodology applied, and conclusions resulting from these data must be reviewed and approved by the CIBMTR statistical staff at least 45 days before any presentation, press release, other display or publication to ensure appropriate interpretation of the analysis and compliance with the terms of this agreement.
- All publications or presentations of these data shall acknowledge CIBMTR as a data source.

- All acknowledgements will be reviewed and approved by CIBMTR prior to submission of the publication.
- All publications will include an acknowledgement of CIBMTR grant support.
- A copy of any abstract, publication or presentation of work derived from these data, along with a complete citation, shall be provided to the CIBMTR within 30 days of its presentation or publication.
- In situations in which the investigator has sufficient data and permission from CIBMTR to combine CIBMTR data with data from another group, the investigator agrees to share the final data file and analysis with the CIBMTR Coordinating Center.
- CIBMTR Guidelines for acquiring PubMed Central Numbers (PMCID) must be followed.

If the intent is for publication, CIBMTR is not involved in the statistical analysis and results will not include clinical interpretation, e.g. a purely methodologic study, CIBMTR will require the following:

- All publications or presentations of these data shall acknowledge CIBMTR as a data source and will acknowledge that the findings presented by the author are not the opinion of the CIBMTR or its funding sources.
- All publications will include an acknowledgement of CIBMTR grant support.
- Notification to CIBMTR if the dataset will be posted with the publication and the duration of the dataset posting.
- In situations in which the investigator has sufficient data and permission from CIBMTR to combine CIBMTR data with data from another group, the investigator agrees to share the final data file and analysis with the CIBMTR Coordinating Center.
- CIBMTR Guidelines for acquiring PubMed Central Numbers (PMCID) must be followed.

By signing this Letter of Commitment, you agree to the terms as outlined above.

This agreement must be signed by you and an "authorized individual" in your institution. In the United States, an authorized individual is a person who can commit for the institution (often an Associate Dean for Research).

Please return this signed Letter of Commitment by the deadline noted in the accompanying email message (includes co-PIs).

Agreed by:

_____ _____

Signature of Individual Authorized to Execute Date

_____ _____

Printed Name of Individual Authorized to Execute Title of Authorized Official

_____

Name and address of recipient institution

_____ _____

Signature of Principal Investigator Date

_____

Request Number

PLEASE FAX SIGNED FORM TO CIBMTR MILWAUKEE CAMPUS: (414) 805-0714
(If you wish to scan, send to contactus@cibmtr.org)

APPENDIX E: CIBMTR CONFLICT OF INTEREST DISCLOSURE FORM

CIBMTR Conflict of Interest Disclosure Form

Collected at the time of journal submission

Manuscript Title: _____

At the time of journal submission, authors are required to disclose any potential conflict of interest, examples include; employment, consultancies, stock ownership, honoraria, paid expert testimony, ownership interests including stock options and/or membership on another entity's Board of Directors or its Advisory Committee.

- You should disclose interactions between yourself, an immediate family member or your institution with ANY entity that could be considered broadly relevant to the work.

- If you have interactions to disclose, report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

- For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

Do you have any relevant conflicts of interest? YES NO

If YES, please list them below:

- Company/Organization:
- Recipient: YOU AN IMMEDIATE FAMILY MEMBER YOUR INSTITUTION

NAME: _____

DATE: _____

SIGNATURE: _____

APPENDIX F: DATA SOURCES STATEMENT

The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program®/Be The Match® and the Medical College of Wisconsin. It comprises a voluntary working group of approximately 420 centers worldwide that contribute detailed data on allogeneic and autologous hematopoietic cell transplantation and cellular therapies. Participating centers are required to report all transplants consecutively; compliance is monitored by CRC staff and patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on site audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable US federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Globally, as required by that country's laws and regulations governing human subjects and privacy protection, the center is responsible for obtaining any necessary institutional review and approval of protocol, "Research Database for Hematopoietic Stem Cell Transplantation and Marrow Toxic Injuries", including the informed consent documents. The center must obtain consent of each patient participating in the research Protocol in a manner consistent with the laws and regulations in effect in that country.

The CIBMTR collects data at two levels: Transplant Essential Data (TED) level and Comprehensive Report Form (CRF) level. The TED-level data is an internationally accepted standard data set that contains a limited number of key variables for all consecutive transplant recipients. TED-level data, with some additional details of donor and graft characteristics, comprise the obligatory data submitted to the SCTOD (Stem Cell Therapeutic Outcomes Database). When a transplant is registered with the CIBMTR, a subset of patients are selected for the CRF level of data collection through a weighted randomization scheme. The CRF-level captures additional patient, disease and treatment-related data. TED and CRF level data are collected pre-transplant, 100 days and six months post-transplant, annually until year 6 post-transplant and biannually thereafter until death.

APPENDIX G: CIBMTR SUPPORT LIST

The CIBMTR is supported primarily by Public Health Service Grant/Cooperative Agreement U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement U24HL138660 from NHLBI and NCI; Grant U24CA233032 from the NCI; Grant OT3HL147741 from NHLBI; Grant R21HL140314 from NHBLI; Grant U01HL128568 from NHLBI; a contract HHSH250201700006C with Health Resources and Services Administration (HRSA/DHHS); Grants N00014-18-1-2888 and N00014-17-1-2850 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals, Inc.; Adaptive Biotechnologies; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; *Anthem, Inc.; Astellas Pharma US; Atara Biotherapeutics, Inc.; Be the Match Foundation; *bluebird bio, Inc.; Boston Children's Hospital; *Bristol Myers Squibb Co.; *Celgene Corp.; Children's Hospital of Los Angeles; *Chimerix, Inc.; *CSL Behring; *CytoSen Therapeutics, Inc.; Dana Farber Cancer Institute; *Daiichi Sankyo Co., Ltd.; Fred Hutchinson Cancer Research Center; *Gamida-Cell, Ltd.; Gilead Sciences, Inc.; *GlaxoSmithKline (GSK); HistoGenetics, Inc.; Immucor; Incyte Corporation; Janssen Biotech, Inc.; *Janssen Pharmaceuticals, Inc.; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals, Inc.; Karius, Inc.; Karyopharm Therapeutics, Inc.; *Kite, a Gilead Company; *Magenta Therapeutics; Medac GmbH; The Medical College of Wisconsin; Mediware; Merck & Company, Inc.; *Mesoblast; MesoScale Diagnostics, Inc.; Millennium, the Takeda Oncology Co.; *Miltenyi Biotec, Inc.; Mundipharma EDO; National Marrow Donor Program; Novartis Oncology; Novartis Pharmaceuticals Corporation; *Omeros Corporation; *Oncoimmune, Inc.; PCORI; *Pfizer, Inc.; *Phamacyclics, LLC; PIRCHE AG; *Regeneron Pharmaceuticals, Inc.; REGiMMUNE Corp.; *Sanofi Genzyme; *Seattle Genetics; *Shire; Sobi, Inc.; Spectrum Pharmaceuticals, Inc.; St. Baldrick's Foundation; Swedish Orphan Biovitrum, Inc.; *Takeda Oncology; University of Minnesota; University of Pittsburgh; University of Texas-MD Anderson; University of Wisconsin – Madison and Viracor Eurofins. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

*Corporate Members

APPENDIX H: CIBMTR NATIONAL INSTITUTES OF HEALTH SUPPORT VERIFICATION LETTER

[DATE]

Dear [NAME],

Thank you for your attention to the enclosed submission. This article is based on research at the Medical College of Wisconsin (MCW) that is funded in whole or in part by grants from the National Institute of Health (NIH) and is therefore subject to the mandatory NIH Public Access policy (See *http://publicaccess.nih.gov/policy.htm*). As a matter of US federal regulation, the final, peer-reviewed manuscript must be deposited with the PubMed Central (PMC) database upon acceptance for publication and be made publicly accessible no later than 12 months after publication. In order to ensure compliance with this mandate and to be sure that copyrights are addressed appropriately, we ask that EITHER:

- You, as the publisher, submit the article directly to PubMed Central after acceptance. In this case, we can work with your standard publication contract and need only ask to be informed when submission is complete so that the required reference number(s) that must be used in subsequent NIH applications can be obtained. OR
- If the necessary language is not part of your standard publication agreement or copyright transfer, please include this additional wording, which is suggested by the NIH: "The Journal acknowledges that Mary M. Horowitz, M.D., M.S. retains the right to provide a copy of the final manuscript to the NIH upon acceptance for Journal publication, for public archiving *in PubMed Central as soon as possible but no later than 12 months after publication by Journal*."

In addition, please inform us of any applicable embargo up to the allowed 12-month delay. We will deposit the article in PMC. It is our hope that one of these options will be employed to ensure that we can cooperate to comply with this mandate. However, since this is a requirement of the current and future NIH funding which supports a great deal of research at MCW, we must ensure that our authors comply with the public access policy. If you accept this article for publication and none of the above options have been implemented, we will ask our authors to include the italicized passage above from the NIH as an additional term of any contract they sign and will proceed with depositing the article in PMC.

Thank you for your consideration and cooperation.

Sincerely,

Mary M. Horowitz, MD, MS

Chief Scientific Director

Center for International Blood and Marrow Transplant Research

APPENDIX I: STUDY DEVELOPMENT CYCLE

This study development cycle pertains to studies for which the CIBMTR provides data and statistical support (**Chapter 6**). Data sets are also made available to investigators who have their own statistical resources (**Chapters 13** and **14**). Manuscripts resulting from these analyses are reviewed and approved by the CIBMTR prior to journal submission (**Chapters 3** and **4**).

PLANNING STAGE

- **Protocol pending**. Proposals remain in this preliminary stage until a draft protocol is created.
- **Draft protocol received**. PI sends a draft protocol to the Coordinating Center.
- **Protocol development**. The PI and invited Working Committee members develop a study proposal into a comprehensive study protocol. The protocol is refined in collaboration with the Working Committee study statistician, Statistical Director, Scientific Director, and Chairs. A table with a preliminary description of the proposed study population is added, and the draft protocol is presented for discussion at a weekly Coordinating Center meeting. When a protocol is approved, Working Committee members are invited to participate in a Writing Committee. Coordinating Center staff use the protocols to prepare data files for analysis and define the detailed study design. This document defines the study and how it progresses.
- **Ongoing**. Ongoing studies are long-term projects that require CIBMTR data and are supported by external funding sources, often multiple grants / renewals. Each study is assigned a Statistical Director.

IN PROGRESS

- **Sample Typing**. During sample typing, the PIs perform laboratory tests (e.g., genotyping) on samples from the Research Sample Repository (**Chapter 7**).
- **Supplemental forms / data collection**. Most CIBMTR studies use routinely-collected data. Use of supplemental data, including data not collected on CRFs (**Chapter 11**), is discouraged unless it will result in a particularly meaningful publication and/or external funding can support the extra burden placed on centers and supplement forms reimbursement costs. If necessary, a supplemental form must be developed and approved prior to soliciting centers for additional data. These forms are prepared by Coordinating Center staff in collaboration with the Principal Investigator and relevant Working Committee Chairs.
- **Data file preparation.** The objective of data file preparation is to create a file of eligible subjects who are consecutively treated at participating centers with adequate follow-up, with minimal missing data fields, and in large enough numbers to give the analysis sufficient statistical power to meet the stated study objectives. This process involves a series of steps by the MS-level Statistician, sometimes working with the Clinical Research Coordinator, to ensure data quality:

  - Verifying selection criteria;
  - Assessing follow-up;
  - Determining the extent and nature of missing values and their potential effects on the study;
  - Resolving and reconciling data discrepancies / outliers by examining data collection forms and communicating with centers and the Principal Investigator;
  - Including and excluding patients so that the investigators can determine whether the final study population is representative of the target population (unbiased sample).
- **Analysis**. Analysis proceeds in several phases. The first generally includes a detailed description of the patient population and univariate analyses of study endpoints. These data are distributed to Writing Committee members for suggestions and comments. An iterative process then ensues, in which the Principal Investigator works with Coordinating Center staff to review comments from the Writing Committee. The process is repeated until final analysis, which serves as the basis for the manuscript.

PRELIMINARY RESULTS

- **Manuscript preparation**. The PI is primarily responsible for manuscript preparation and is expected to prepare a draft manuscript. The manuscript is distributed to Writing Committee members for suggestions and comments. An iterative process then ensues, in which the PI works with Coordinating Center staff to review comments from the Writing Committee. The process is repeated until manuscript is ready for submission. See **Chapter 3** for detailed guidelines regarding authorship.
- **Submitted**. Coordinating Center staff are generally responsible for submitting the manuscript and corresponding with the chosen journal. The Working Committee Scientific Director often serves as corresponding author. See **Chapter 4** for detailed guidelines regarding manuscript submission.
- **In press**. A publication is in press when it has been approved but does not yet have a citation.

COMPLETED

- **Published**. A manuscript is considered published when a citation is available, including a PubMed Central Identification (PMCID) number, if applicable. See **Appendix C** for detailed guidelines regarding PMCIDs.

APPENDIX J: RESPONSIBILITIES OF BMT CTN DATA AND COORDINATING CENTER (DCC) MEMBERS

The CIBMTR shares administration of the DCC with NMDP/Be The Match and The Emmes Company, a contract research organization. The following table shows the shared responsibilities of these organizations. This table is maintained and updated in the BMT CTN Manual of Procedures, available at the *BMT CTN* website.

DCC Member Responsibilities	CIBMTR	NMDP/ Be The Match	Emmes
Administrative Functions			
Provide overall scientific /administrative leadership	Lead		
Develop statistical methodology[1]	Shared		Shared
Recruit, manage, and train pool of physician Medical Monitors	Lead		
Develop Manuals of Procedures / Standard Operating Procedures (SOPs)			Lead
Facilitate meeting logistics (including site location, travel arrangements, conference calling, travel reimbursement)		Lead	
Coordinate meeting materials[2]		Shared	Shared
Manage general and study-specific electronic communications (including clinicaltrials.gov posting, numbered memoranda, websites)			Lead
Maintain master rosters			Lead
Prepare protocol budgets and track protocol-specific financials		Lead	
Monitor overall budget and subcontracts	Lead		
Trials Development & Management			
Develop / review concepts[3]	Shared	Shared	Shared
Develop protocols[3]	Shared	Shared	Shared
Protocol Team			
Serve as Protocol Officer	Lead		
Serve as Protocol Statistician[1]	Shared		Shared
Serve as Protocol Coordinator		Shared	Shared
Protocol Implementation			
Manage protocol document and all amendments		Shared	Shared
Identify centers	Lead		
Qualify centers (certify centers' ability to execute protocol)			Lead
Contract with centers		Lead	
Identify and contract laboratories / repositories		Lead	

DCC Member Responsibilities	CIBMTR	NMDP/ Be The Match	Emmes
Template regulatory forms (1572, financial disclosure, site delegation log)		Shared	Shared
Manage data management system (including registration, Web-based data entry, database design, study archive backup, contingency plans)			Lead
Develop Case Report Forms			Lead
Coordinate laboratory and repository functions		Lead	
Manage investigational product distribution[4]		Shared	Shared
Prepare and submit IND/IDE applications and reports to the FDA			Lead
Prepare materials and provide Protocol Review Committee and Data and Safety Monitoring Board meeting support		Shared	Shared
Manage site activation process		Shared	Shared
Train site personnel		Shared	Shared
Develop informed consent forms and patient materials		Lead	
Develop study-specific handbooks and/or SOPs for processes, lab samples, investigational product, and data management[5]		Shared	Shared
Monitor adverse events, toxicities, and other safety endpoints			Lead
Develop and implement accrual plan[6]	Shared	Shared	Shared
Review performance of centers[7]	Shared	Shared	Shared
Monitor accrual[8]	Shared	Shared	Shared
Develop site monitoring plan, conduct monitoring visits, write monitoring reports, and manage corrective action plans			Lead
Monitor data accuracy and conduct data review sessions[9]			Lead
Prepare reports / manuscripts / coordinate dissemination of results[10]	Shared	Shared	Shared

1 ~75% of PhD Protocol Statisticians are CIBMTR staff members and 25% Emmes staff members; Emmes MS-level statisticians provide primary support for data set preparation and Data Safety and Monitoring Board reports. CIBMTR MS-level statisticians help with data transfer, concept evaluation, accrual plans and assessment of ongoing accrual.

2 NMDP/Be The Match staff members develop agendas and supporting materials and finalize minutes for Steering and Executive Committee meetings and DCC calls; Emmes staff members develop agendas, supporting materials, and reports for the Protocol Review Committee and Data and Safety Monitoring Boards. Both organizations contribute to protocol team call agendas, materials, and minutes.

3 Key personnel from all three entities review protocol concepts. The CIBMTR provides HCT data to assess feasibility; Emmes and CIBMTR statisticians draft statistical plans. Protocol teams include a CIBMTR

Protocol Officer, Emmes Protocol Coordinator, and CIBMTR or Emmes Statistician with support from Emmes Safety Monitors and from NMDP/Be The Match Contracts, Patient Services, and Immunobiology staff members.

4 NMDP/Be The Match develops and executes agreements for investigational agents. NMDP/Be The Match and Emmes work together to implement distribution of investigational agents as per the contract and project sites' needs.

5 NMDP/Be the Match prepares study-specific handbooks and/or SOPs for lab samples and investigational products as well as patient-specific materials. Emmes and NMDP/Be The Match prepare study-specific site SOPs and activation materials.

6 The accrual plan is drafted by the NMDP/Be The Match Project Manager / Accrual Coordinator based on projected accrual rates from Core and Affiliate Centers, data from the CIBMTR Research Database, and input from the Protocol Team.

7 Accrual, data delinquency, missing values, and data queries in AdvantageEDC, Advantage eClinical, and CIBMTR FormsNet, data discrepancies, and major and minor protocol violations are tracked by Emmes and NMDP/Be The Match. NMDP/Be The Match monitors sample collections and lab testing compliance. The CIBMTR monitors data submitted via FormsNet to the CIBMTR which is not captured by AdvantageEDC or eClinical. Emmes prepares annual center performance reports and NMDP/Be The Match and Emmes prepare quarterly center performance reports that are sent to Core Centers.

8 Emmes monitors and posts daily accrual to each protocol by center. The NMDP/Be The Match Project Manager / Accrual Coordinator surveys centers for estimated accrual to each study and then monitors center accrual against projections. The CIBMTR uses its Research Database to assess and address accrual issues.

9 The CIBMTR Protocol Officer also has a key role in coordinating the Endpoint Review Committee.

10 The Protocol Coordinator, Officer, and Statistician all contribute to preparation of presentations and publications. Emmes provides administrative support to the Publications Committee in its oversight of the publication process. NMDP/Be The Match Contracts staff assures proper acknowledgement of trial contributors. CIBMTR, NMDP/Be The Match and Emmes staff members coordinate, compile, and distribute the annual BMT CTN Progress Report to the research community and the public to provide them with results from presented and published studies and updated information on protocol activity.

APPENDIX K: STANDARD OPERATING PROCEDURES (SOP) INDEX

Following is a list of CIBMTR standard operating procedures (SOPs) referenced in this Manual of Operations. For more information regarding CIBMTR SOPs, email contactus@cibmtr.org.

Chapter	SOP Title	SOP Number
1. Organization	N/A	
2. Committee Structure	CIBMTR Conflict of Interest Policy	POL-0001
	CIBMTR Conflict of Interest Survey	Form-0001
3. Authorship	Manuscript Preparation	SOP-0072
4. Manuscript Submission	Manuscript Submission	SOP-0073
5. Statistical Resources	N/A	
6. Clinical Outcomes Research	CIBMTR Data Sharing to Non-CIBMTR or Non-NMDP Employees	SOP-0069
	Time Tracking SOP	SOP-0152
	Statistical Meetings	SOP-0068
	Approval of Working Committee Studies	SOP-0067
7. Immunobiology Research	N/A	
8. Clinical Trials Support	N/A	
9. Health Services Research	N/A	
10. Bioinformatics Research	N/A	
11. Data Management	Scheduling Transplant Center Audits	SOP-0149
	Transplant Center Audit Preparation	SOP-0150
	Transplant Center Audit Process	SOP-0151
12. Human Research Protection Program	N/A	
13. Data – Access and Release	Data Release Policy	POL-0003
	Linking Data to External Databases or Data Sources	SOP-0100
14. Information Technology Services	CIT System Development Lifecycle	SOP-0125
	Data Retrieval	SOP-0048
	DBTC Quarterly SAS Data Load Process	SOP-0050
	eDBtC Monthly Load Process	SOP-0051

Chapter	SOP Title	SOP Number
14. Information Technology Services (continued)	Survival Calculator Information and Update Process	SOP-0055
	Refresh Data for Center Performance Analytics	SOP-0117
	Maintaining CIT Information System Inventory	SOP-0160
	FormsNet3 Account Management	SOP-0163
	CIBMTR Incident Response Plan	Plan-0002
	Incident Response for Data/Systems Policy	POL-0019
	Vulnerability Scanning and Remediation	SOP-0059
	Configuration Management for Systems/ Data	POL-0009
	CIBMTR Contingency Planning Policy	POL-0018
	Security Awareness and Training Policy	POL-0005
15. Communication	CIBMTR Research Publication Summaries for Patients	SOP-0024
	CIBMTR Annual Progress Report	SOP-0037
16. Meetings	N/A	
17. Growth and Development: Non-Federal Funding	N/A	
18. Finance Management: Federal Funding	N/A	

Document History

Date	Version	Description of Changes	Completed By
9/27/2012	1.0	First edition (posted to website)	Paula Watry
10/11/2012	1.1	Posted CIBMTR Advisory Committee review	Paula Watry
3/12/2013	1.2	Revised International Organizations with which the CIBMTR Collaborates (Table 20.1) Revised Letter of Commitment to Complete CBMTR Observational Study (Appendix D1) Revised Letter of Commitment for the Use of CIBMTR Datasets (Appendix D2)	Paula Watry Waleska Perez Doug Rizzo
7/1/2015	2.1	Reviewed and updated entire document	Vicki Vlach Jessica Gillis-Smith Patty Steinert
8/12/2016	3.1	Reviewed and updated entire document Added Working Committee Efficiency (Section 6.1.3) Added Bioinformatics Research (Chapter 10)	Jessica Gillis-Smith Waleska Perez Michael Wright Patty Steinert
7/1/2017	4.1	Reviewed and updated entire document Added Cellular Therapy Reporting (Section 12.2.3) Added Consolidation of FACT-CIBMTR Audits (Section 12.7.2.1)	Andrea Kusch Jessica Gillis-Smith Patty Steinert
7/21/17	4.2	Added HRSA Security Assessment SOP (Appendix M)	Jessica Gillis-Smith Patty Steinert
7/1/18	5.1	Reviewed and updated entire document Added SOP references Added CIBMTR Data Release Policy (Section 15.2.2) Added Electronic Patient Reported Outcomes (Section 15.2.1.1.3) Added Appendix M: Standard Operating Procedures	Andrea Kusch Jessica Gillis-Smith Patty Steinert
8/13/19	6.1	Reviewed and updated entire document Added additional SOP references and numbers Add Cellular Therapy Research (Section 6.3), CMS CED Studies (Section 6.4), and PRO (Section 6.5) Restructured Appendix K: SOP Index	Liz Siepmann Jessica Gillis-Smith Patty Steinert